Aberrant Salience and the Risk of Psychosis

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Declaration

I confirm that the following thesis does not exceed the word limit prescribed in the College regulations. I further confirm that the work presented in the thesis is my own and all references are cited accordingly.

Tobias Thomas Winton-Brown

7 September 2012

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Finally I would like to thank my own family, and my wife Ana, who watched this all unfold, and still stuck around. This is dedicated to her.

Abstract

This study unpacks the concept of 'salience' as invoked by Kapur and others in linking dopamine dysregulation to psychotic symptoms. Rather than relying on unidimensional reward based conceptions that have dominated empirical studies thus far it reconsiders the notion from a healthy salience processing point of view. It sets out to then test this model using fMRI and PET scanning in unmedicated subjects at high clinical risk for psychosis in the neural setting of a subcortical and network derived from the MAM animal model of schizophrenia.

To do this I developed a factorial fMRI task that incorporates probes of Novelty and Emotion alongside aspects of Reward. I found behavioural and fMRI main effects and interactions of each aspect in a sample of 29 healthy controls, and used this to advance a multidimensional framework of normal salience processing. We then found several specific departures from this framework in a sample of 29 participants with an At Risk Mental State for psychosis, particularly in the domains of reward and in the interactions with emotion. This resonates with the affectively laden altered motivational states seen in early psychosis and described by early phenomenologists, and fits with cognitive models that emphasise the importance of emotion in producing psychotic symptoms.

Finally, in half of the sample we additionally obtained ^{18}-F-DOPA PET scans and found altered relationships between hippocampal activation to salient stimuli and striatal presynaptic dopamine synthesis in high risk subjects compared to controls. These were as predicted by the MAM model.

These findings add support to aberrant salience models of early psychosis and demonstrate that abnormalities in salience processing are present prior to the onset of the first psychotic episode. They also support predictions from the MAM model of schizophrenia that suggests ventral hippocampal overdrive may provoke hyperdopaminergia in psychosis. They therefore also point towards this upstream target for potential new treatments. This will form the basis of ongoing work.

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1. Introduction

1.1 Psychosis

1.1.1 Overview

> *'The most profound distinction in psychic life seems to be that between what is meaningful and allows empathy and what in its particular way is ununderstandable, 'mad' in the literal sense, schizophrenic psychic life'*
>
> Karl Jaspers, General Psychopathology (Jaspers, 1966)

The experience of psychosis, with its distortion of reality, beliefs, perception and behaviour has historically confounded ordinary empathetic attempts to understand it. Early accounts invoked a possession of the sufferer by malign spirits. Kraepelin considered psychosis as sign an early deteriorating brain illness, *dementia praecox*. Bleuler, influenced by Freud, conceived of *schizophrenia,* a splitting of basic psychic functions. Jaspers followed, and his distinction between affective illness and psychosis held popular and professional sway for the greater part of last century, and reflected wider views of 'madness' as categorically different to ordinary human experience; fascinating and frightening. However an appreciation of the spectrum of psychotic-like experiences in non-clinical populations (van Os, Hanssen, Bijl, & Ravelli, 2000) and new cognitive models of understanding the development of psychotic symptoms are beginning to bridge this *ununderstandable* divide.

Alongside these is considerable progress in cataloguing the biological changes accompanying the development of psychotic symptoms, anchored in a greater understanding of the normal

functioning of the human brain. The framework that links such understanding with cognitive models of normal and diseased brain states is provided by Cognitive Neuropsychiatry (David, 1993). Such an approach is distinguished by an insistence on understanding clinical symptoms (rather than diagnoses) in terms of damage to normal information processing systems (such as memory, perception, attention, emotion), and their underlying neural substrates (including lesions, neurochemical changes and network disturbances). It attempts to stride the explanatory gap between 'brain-level' biological findings and abnormal 'mind-level' phenomena by first being firmly grounded in both (David & Halligan, 2000). These will be considered in turn.

1.1.2 Phenomenological characteristics of early psychosis

Early descriptions of the development of psychotic symptoms come from retrospective interviews of patients and caregivers - this method was used by phenomenologists such as Kraepelin (1919), Bleuler (1950), Conrad (1958), Meares (1959) and Bowers (Bowers & Freedman, 1966). Klaus Conrad's main contribution focused on the earliest experiences of psychosis, prior to and during the formation of delusional beliefs and hallucinations (Bush & Luu, 2000; Mishara, 2010). His descriptions predated the recent upsurge of prospective research in prodromal psychosis by some 40 years, but resonate well with such recent accounts. In the first of Conrad's 3 stages, delusional mood or '*Trema*" precedes the onset of delusions by a period of days, months or even years. The feeling at this time is of expectancy, that something is about to happen, alongside a "marked change in motivational and emotional state" (Mishara, 2010). He describes this as first associated with the *most salient* experiences, but eventually spreading to pervade the patient's entire experiential field. This becomes imbued with the theme of the incipient delusion, and has a transformed "physiognomic'"

quality that is accompanied by affective tension. Such descriptions chime with other first-hand accounts of this early period of psychosis (Stanton, 2000), such as those recorded by Bowers (1966):

> *"I was in a higher and higher state of exhilaration and awareness. Things people said had hidden meaning. They said things that applied to life. Everything that was real seemed to make sense. … My senses were sharpened. I became fascinated by the little insignificant things around me…*
>
> *"Thoughts spun around in my head and everything—objects, sound, events—took on special meaning for me. ..*
>
> *…my senses were sharpened, sounds were more intense and I could see with greater clarity, everything seemed very clear to me. Even my sense of taste seemed more acute...." (Bowers & Freedman, 1966)*
>
> *"Every single thing "means" something…"(Brundage, 1983)*

There is also often a misplaced sense of recognition, and familiarity:

> *"..a patient with incipient schizophrenia is placed temporarily in a guardhouse before transport. Being a former carpenter, the patient finds that the door, windows, floorboards, and bed frame in the cell have a ''familiar'' quality." (Mishara, 2010)*

The 2nd stage, *apophany* (revelation), comes as an *Aha*-experience whereby delusions appear as a relieving explanation for what had been a series of perplexing and disturbing experiences, and often involve the self as a central reference point of the universe (*anastrophe*).

> *"..He sees all at once that he himself is the carpenter of these objects. They look so familiar. They were removed from his old workshop. The windowsill has scratches on it, which he made as a child and has been removed from his childhood home…*

"I felt like I was putting the pieces of a puzzle together…I increasingly began to feel that I was experiencing something like mystical revelations…

"..Things began to fall together and make sense…" (Mishara, 2010)

In emphasizing the altered perceptual field Conrad's account is distinct from two-stage models where abnormal meaning is inexplicably attached to an otherwise normal perception, such as described by Jaspers or Schneider (Uhlhaas & Mishara, 2007). It also resonates with historical descriptions of late prodromal states for psychosis (Yung & McGorry, 1996a) that led to formalized criteria for clinical 'high risk' states (Yung & McGorry, 1996b)

1.1.3 The context of psychosis

Psychosis often occurs in the context of schizophrenia - a relatively common, markedly disabling and costly condition which has positive psychotic symptoms as its hallmark: chiefly hallucinations (aberrant perceptions), delusions (fixed, false beliefs) and thought disorder (van Os & Kapur, 2009). Schizophrenia also often presents with negative symptoms (such as problems with volition and affect) and cognitive symptoms (e.g. memory and executive dysfunction), that can be particularly disabling and enduring. Psychosis also occurs in the context of other mental illnesses, particular bipolar affective disorder, and also in physical illness, and remains difficult to diagnose and treat. By the onset of the first psychotic episode there have already been substantial decreases in social and occupational function accompanied by significant structural and functional brain changes (Velakoulis et al., 2006). Prediction and prevention of this first episode is therefore of paramount importance (McGorry, 2008).

1.1.4 Prodromal psychosis and the At Risk Mental State

Key to this enterprise is the identification of high-risk samples, such as those characterized by genetic loading and attenuated psychotic symptoms (Yung & McGorry, 1996a). In the 1990s in Melbourne Yung et al developed criteria that permit sampling of a clinical 'Ultra-High Risk' (UHR) population with an untreated transition rate to psychosis of between 35-54% over a 1-2 year period (Yung et al., 2003; 2005). Several other sets of criteria have evolved since (Olsen & Rosenbaum, 2006a) and the validity of the construct has now been established in a number of independent prospective cohorts (Olsen & Rosenbaum, 2006b) with psychosis prodrome clinics and research services world wide (Liu et al., 2010).

This At Risk Mental State (ARMS) for psychosis is phenomenologically characterized by attenuated positive psychotic symptoms such as hallucinations and delusions, non-specific psychiatric symptoms such as depression and anxiety and a range of detectable neurocognitive deficits (Seidman et al., 2010; Yung & McGorry, 1996b). Later states in the prodrome are characterized by a perplexingly altered sense of novelty, emotion and personal significance, just prior to the onset of frank psychosis, that recall descriptions by phenomenologists such as Conrad's 'Trema' (in 1.1.2).

However, predicting transition to psychosis is difficult on the basis of clinical features alone, and research towards this end has grown steadily. Prospective studies exploring vulnerability to psychosis are powerful in this regard as many of the detectable changes in brain structure and function occur before the onset of the first episode and subjects are usually free of the confounding effects of medication (Olsen & Rosenbaum, 2006b).

As well as understanding 'mind-level' phenomenological characteristics of psychosis, an effective CNP model also requires an understanding of the 'brain-level' findings that accompany it.

1.1.5 Overview of brain changes in psychosis

Brain changes in psychosis have been posited since Kraepelin and Alzheimer's first neuropathological investigations (Harrison, 1999; 1919). Following the CT demonstration in 1976 of enlarged lateral ventricles in chronic schizophrenia (Johnstone EC, 1976) there has been an upsurge in in vivo imaging studies showing such brain changes (Bora et al., 2011). These include samples in first episode psychosis and high risk samples that minimize the effects of illness chronicity and medication. Most consistently demonstrated are enlarged ventricles and reductions in medial and superior temporal lobes (Honea, Crow, Passingham, & Mackay, 2005)and there have been several demonstrations of dynamic progressions in these changes prior to (Pantelis et al., 2003) and following disease onset (Kempton, Stahl, Williams, & Delisi, 2010).

Functional brain studies, mostly employing cross sectional fMRI designs, demonstrate differences in those with psychosis from controls in a range of general cognitive tasks spanning learning, memory, perception, emotion, and executive function and implicate areas such as the prefrontal and anterior cingulated cortex, the basal ganglia, medial temporal lobes and cerebellum (Fusar-poli et al., 2007). Such altered function is proposed to reflect basic mechanisms of disease. Deficits in working memory and prefrontal cortex (PFC) inefficiency for example have been proposed as intermediate phenotypes for psychosis (reviewed in Meyer-Lindenberg & Weinberger, 2006); unaffected siblings and co-twins and those with an

ARMS share qualitatively similar deficits of a lesser extent (Broome et al., 2009). Despite these there have been relatively few findings with consistent associations with either a risk state or a first episode of illness, reflecting inconsistencies in scanning protocols, sample and illness definitions, low sample size and also the tasks used which usually employ well validated cognitive paradigms rather than tasks specifically tailored towards testing specific cognitive models of psychotic symptoms (Fusar-Poli, Allen, & McGuire, 2008),.

Neurochemical brain imaging techniques such as Positron Emission Tomography (PET) and Magnetic Resonance Spectroscopy (MRS) allow exploration of alterations in neurotransmitter systems in psychosis. Evidence for the long standing dopamine hypothesis of psychosis (recently reviewed in Howes & Kapur, 2009) comes first from studies of the function of early antipsychotics, reserpine, amphetamine, and the relationship between antipsychotic efficacy and D2 receptor blockade . Further evidence from PET and SPECT studies has shown increased striatal dopamine synthesis and release (via increased ligand displacement following amphetamine challenge), increased occupancy of D2 receptors (via a dopamine depletion technique) and a possible modest elevation in striatal D2/3 receptor density (Howes et al., 2012; reviewed in McGuire et al., 2007). There is also some support for the proposal that prefrontal hypodopaminergia underlies the cognitive symptoms in schizophrenia although this less consistent (Abi-Dargham & Moore, 2003). Increased pre-synaptic dopamine synthesis has also been demonstrated in subjects with prodromal signs of psychosis (Howes et al., 2009). These findings will be reviewed in further detail below.

Opponents of an exclusively dopamine oriented hypothesis of psychosis point to inadequacies of dopamine blocking medication in fully treating psychosis, the failure of dopamine based pharmacological models to reproduce negative and cognitive symptoms of psychosis, and to

candidate genes for schizophrenia that affect alternative neurotransmitter systems (reviewed in Stone, Morrison, & Pilowsky, 2007). Instead models derived from the effects of ketamine and phencyclidine (PCP) and based on NMDA and GABA receptor dysfunction are proposed: hypofunction of receptors on GABA interneurons lead to a loss of tonic inhibition on glutamatergic axonal projections and result in excitatory neurotoxicity and the structural changes seen on imaging and post mortem (Olney, Newcomer, & Farber, 1999). Support for this model comes from in vivo MRS studies demonstrating for example elevated glutamine in the anterior cingulate cortex in healthy subjects following ketamine administration and in first episode psychosis, and from SPET studies using ^{123}I-CNS-1261 demonstrating reduced NMDA receptor availability (Olney et al., 1999). Also relevant are MRS studies demonstrating differences in anterior cingulate and thalamic glutamate/ glutamine levels in genetic and clinical high risk samples, the latter also relating to changes in grey matter volume (Stone et al., 2009). Such evidence suggests that whilst dopamine dysfunction may be the 'final common pathway' for psychosis (Howes & Kapur, 2009) GABA or glutamate dysfunction may be lie pathophysiologically 'upstream'. Possibilities for new directions in pharmaceutical development that proceed from this model are thus promising but are as yet unfulfilled (Stone & Pilowsky, 2007).

Aside from imaging, neurophysiological studies have demonstrated abnormalities suggesting problems with to sensory filtering, such as impaired prepulse and latent inhibition (Swerdlow et al., 2006) and reduced P50 and P300 cortical evoked potentials (Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004), and reduced gamma-band synchrony, suggestive of brain dysconnectivity (Uhlhaas, Haenschel, Nikolić, & Singer, 2008).

While there have been significant advances in the understanding of the neurobiology of psychosis, many mysteries remain; we do not yet understand how a change in dopamine signaling can lead to paranoid and bizarre beliefs. Key to this is the link between 'brain-level' neuroscience findings, such as those described above, and 'mind-level' explanations of patients' experiences. Research within a CNP framework, that applies theoretically driven models of cognitive function and their neural basis to the understanding of symptoms, can help make this link.

1.2 Cognitive model of psychosis

1.2.1 Overview

Cognitive models of psychosis share an emphasis on pre-existing beliefs and ongoing appraisal of experiences in generating symptoms. In an individual with biopsychosocial vulnerability, stress for example may trigger emotional and cognitive changes that lead to anomalous experiences. Hemsley and colleagues suggest that such anomalous intrusions into conscious awareness arise from deficits in moment-by-moment integration of new input with stored memories (Gray, Feldon, Rawlins, Hemsley, & Smith, 1991; Hemsley, 1993), while Frith, who focuses on anomalies of the awareness of self-generated thoughts or actions, relates these to deficits in self-monitoring (Frith, Blakemore, & Wolpert, 2000). Following this, Garety and colleagues suggest that specific reasoning and information processing biases, pre-existing schematic beliefs about the self and others, emotional disturbance and social factors both singly and in combination facilitate appraisals of the origins of these anomalous

mental states as external. This results in the abnormal beliefs and hallucinations becoming symptomatic (Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001).

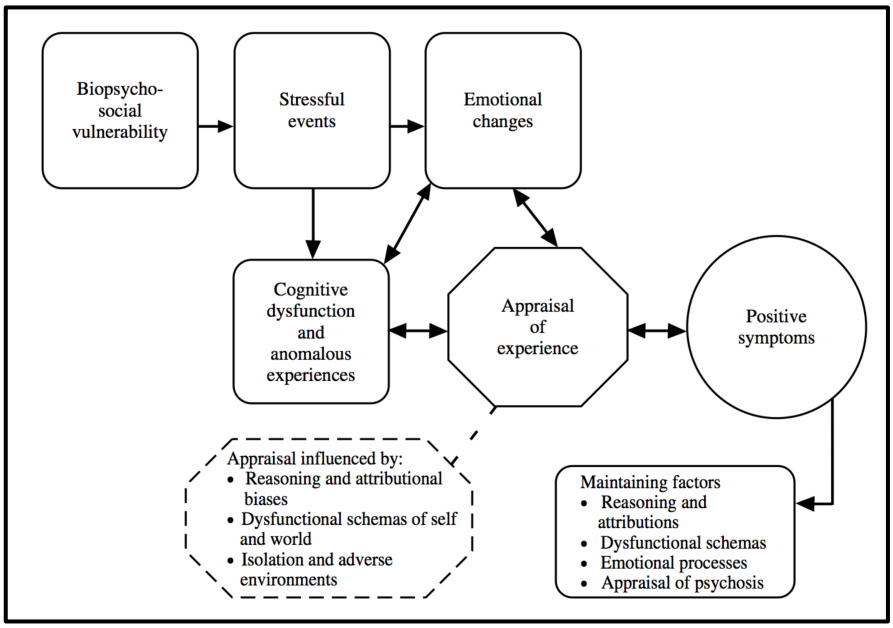


Figure 1.1 Cognitive models of psycohsis emphasise the importance of prior vulnerabilities, emotional changes and appraisal of anomalous experiences in generating and maintaining psychotic symptoms (adapted from Garety et al., 2001)

However such cognitive models rarely incorporate neurobiological findings into how the occurrence of anomalous experiences and the development of psychotic symptoms is instantiated in the brain.

1.2.2 Aberrant salience and the onset of psychosis

One influential account along these lines proposes that the aberrant assigning of "salience" to otherwise innocuous stimuli is fundamental to the development of psychosis, and reflects the dysregulation of striatal dopamine function associated with the disorder. According to this model, overdriven or noisy meso-cortico-limbic dopamine signalling leads individuals in the

prodromal phase of the disorder to attach meaning to what would normally be bland or undetected external and internal sensory events, such that they seem new and significant and form the basis of delusional beliefs and hallucinations (Kapur, Mizrahi, & Li, 2005a).

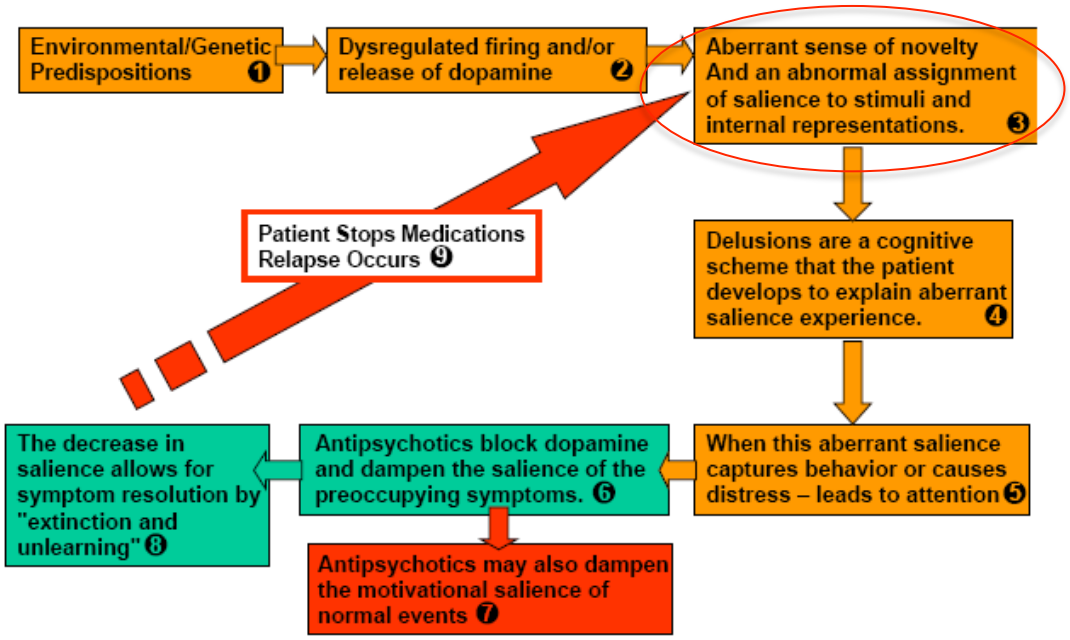


Figure 1.2 - Model 1: Aberrant Salience Hypothesis (from Kapur, Mizrahi, & Li, 2005a). Individuals in the prodromal stages of psychosis (circled) experience distressing and aberrant prominently salient experiences, which can lead to odd beliefs.

The "aberrant salience hypothesis" (figure 1.2) evolved from prior work on the normal function of dopamine and its role in addictive behaviours, in particular reward anticipation, sensitization and reward dependent learning and motivation, and also from earlier cognitive accounts of the formation of psychotic symptoms emphasising failure of integration of past memories and current sensory inputs (Gray et al., 1991). This model resonates with both patient and physician accounts of early psychosis previously described above and has become influential even to the extent of a suggested renaming of the disorder (van Os, 2009). This is

reflected in the increased number of studies involving salience or related concepts in recent years. A PubMed search of the term 'salience' reveals greatly increased returns year on year, including when limited to the fields of medicine, psychology or neuroscience (figure 1.4)

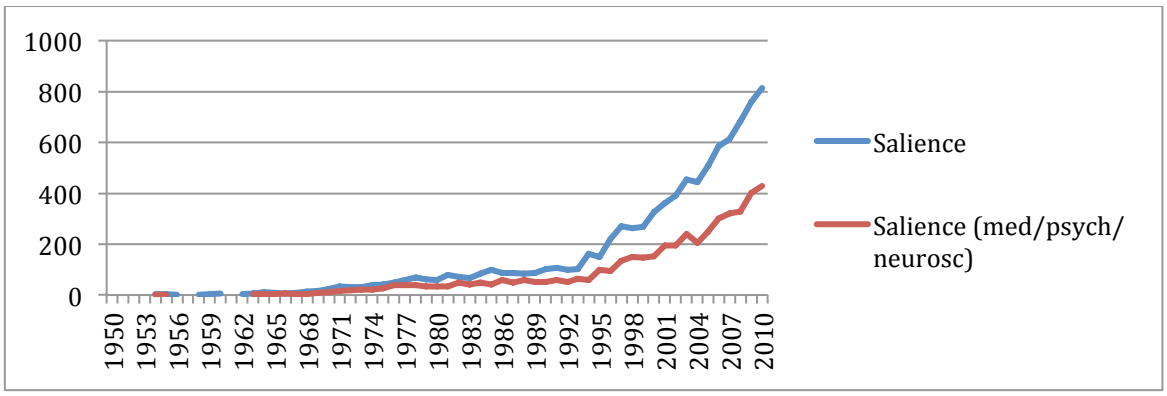


Figure 1.3 - Year on year pubmed searches of 'Salience' overall (blue) and constrained by research fields Medicine Psychiatry, or Neuroscience (red)

For specialised psychosis researchers it is also worth noting that 'salience' is also invoked in research related to other major psychiatric illness, particularly addictive and mood disorders. Figure 1.4 displays year on year PubMed searches of the term 'salience' in combination with terms related to addictive, affective and psychotic disorders.

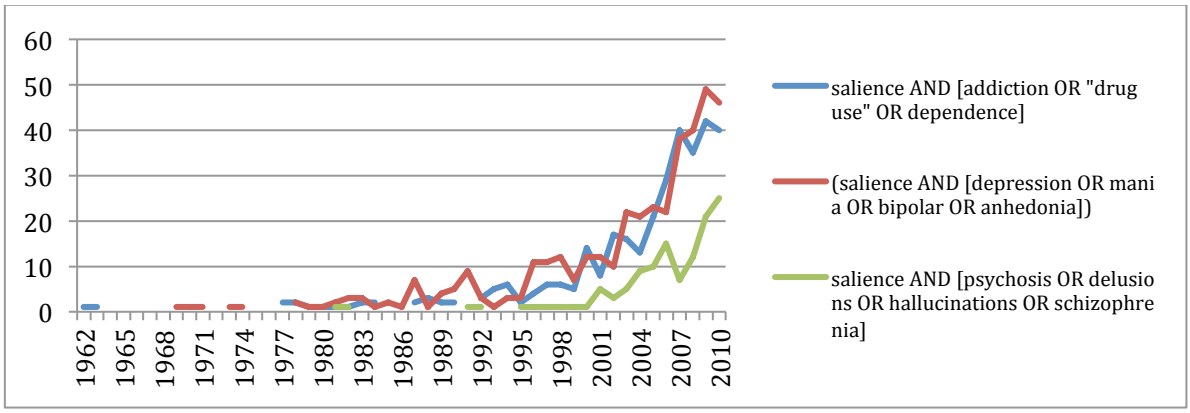


Figure 1.4 - Year on year pubmed searches of 'Salience' and related terms

What is unspecified by this aberrant salience model of psychosis however, and what is confounded in subsequent empiric investigations of salience processing in psychosis, is what precisely is meant by 'salience'. While this model broadly conforms to a CNP framework - linking abnormal symptoms of the mind to biological changes in the brain via dysfunction in a known cognitive system - it leaves out exactly which aspects of this system - *salience processing* - are altered, and how. In this critical sense function must be understood prior to dysfunction.

1.2.3 What is Salience? Perceptual salience, attention and goal directed behaviour

The broad challenge for any organism negotiating a sensorially cluttered and complex world is how to efficiently and effectively choose and respond to relevant stimuli, whether predator prey or potential mate. The world is complex and the demands of limitless perceptual inputs compete for limited cognitive resources, which must be allocated according to some priority. This allocation involves the processes of attention: filtering, sensory and behavioural orientation, active searching, and the processes of response: selection, command, execution and monitoring. The 'spotlight' of attention extracts and processes more information from attended stimuli while others fade into the background (Crick 1984). Stimuli are prioritised according to their 'saliency'- their features compared to their context.

For vision certain physical features tend to be reliably salient (Nothdurft, 2000); movement, colour, contrast, and orientation combine in a topographic 'saliency map' of perceptual features within a scene that draw attention, (Koch and Ullman 1985, example figure 1.5).

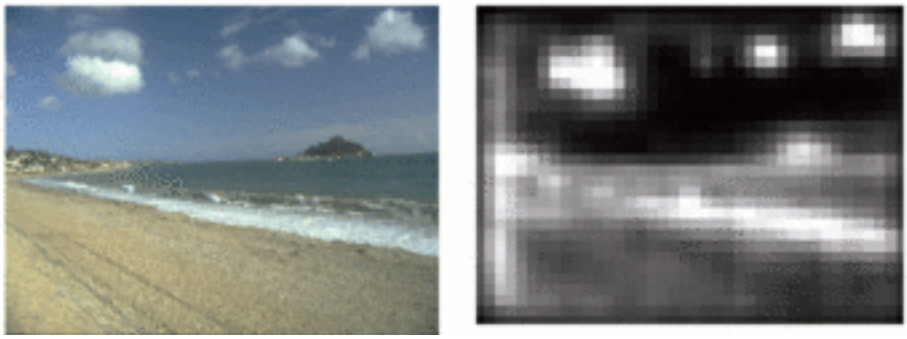


Figure 1.5 Visual scene (left) and example corresponding saliency map (from http://www.scholarpedia.org/)

Analogous features exist in other senses and highly salient stimuli, such as a loud bang or a flash of light, are attended to largely independent of the organism state. Mostly however, such physical stimulus driven processing interacts with internal factors of the organism- goals, beliefs, history and so on to determine the most salient stimulus at a given point in time and place for a given organism. A hungry animal will mostly ignore everything that is not the sight, sound or smell of prey unless an unexpected, novel and potentially dangerous event such as the sound or shadow of a bird of prey overhead overrides the search.

Two interacting processes of stimulus-driven and goal-directed attentional control are thought to relate in part to different neural networks centred on the dorsal posterior parietal - superior frontal cortex, and the ventral temporo-parietal and inferior frontal cortex, respectively (Corbetta and Shulman 2002). Disruptions in either such as in parietal stroke can lead to unilateral spatial neglect.

Salient stimuli in humans are ones therefore that grasp and alter attention, thought and behaviour, processes that are also driven in part by the actions of dopamine.

1.2.4 Motivational salience: reward prediction, threat prediction, prediction error and learning

A key influence on goal-directed behaviour is the active pursuit of reward and the avoidance of punishment. 'Reward' here refers to the positive value given to an object, a behavioural act or an internal state; rewards reinforce the behaviour that led to them. The role of dopamine has received particular attention in this context: drugs of addiction are thought to function by increasing or prolonging the action of dopamine in its main projection targets. Animals with electrodes planted in these areas will repeatedly choose to self- stimulate these over food and sex, sometimes until death (Olds, 1958). While initial studies focused on the role of dopamine in the actual experience of pleasure (Wise & Rompre, 1989), Berridge and Robinson (1998) subsequently separated reward into 'wanting' (*incentive salience*), 'liking' (*hedonic impact*) and 'learning' (*reward learning*). In a series of influential experiments in dopamine depleted rats they argued that dopamine is necessary only for the former, i.e. that dopamine systems mediate the motivational significance of rewards – the willingness to work for them - rather than the pleasure they provide or the learning that results (see also Flagel 2011).

A further insight came from Schultz and colleagues (1997), recording individual dopamine neuron output in primates, who highlighted the intimacy of prediction and reward in driving instrumental learning. While phasic dopamine responses do occur to unpredicted rewards they are absent when predicted by a conditioned stimulus for that reward and instead transfer to the predictor, signaling the anticipation of reward, as opposed to the reward itself. The explanation is that when an expected reward fails to occur, dopamine neurons are inhibited. Learning is driven by the mismatch between prediction and outcome, or prediction error, quantified by for example Temporal Difference computational models that account for the

uncertainty, magnitude and timing of rewarding outcomes (Schultz 1997). Large prediction errors, represented by large phasic dopamine signals, are highly salient, leading the organism to adjust behaviour and cognition at ascending hierarchical scales (Fletcher, Friston 2009).

The extent to which dopamine responses are restricted to reward is the subject of ongoing debate (e.g. Ungless 2004, Redgrave 1997, Schultz 2010). In human fMRI studies dopaminergic regions also appear to be activated in response to aversive stimuli and their anticipation (Carter 2009), and cell recordings in rodents and primates have demonstrated increased phasic output from dopaminergic regions to aversive stimuli (Mantz 1989) as well as a slower output component that responds to aversion and risk (Thierry 1976). This leads to a broader consideration of non-reward aspects of salience (Horvitz 2000).

1.2.5 Non-reward aspects of salience: novelty and emotion

While the role of dopamine in reward prediction error based associative learning has broad support (Schultz, 1997; 2010), the timing of phasic dopamine output following a sensory event (50-100ms) precedes the attentive sensory processing, including gaze-shifting, required to make an accurate reward prediction, which therefore remains unknown at the time of dopamine signaling (Redgrave 2006). Redgrave and colleagues suggest that the function of dopamine output is instead to reinforce behaviours associated with salient sensory input, promoting a sense of agency and guiding the discovery of new actions (Redgrave & Gurney, 2006; Redgrave, Vautrelle, & Reynolds, 2011). Dopamine neurons indeed respond to a range of novel stimuli regardless of their appetitive or aversive consequences (Heinz, Grace, & Beck, 2009), and novel stimuli elicit reliable orienting and approach/avoidance responses in most species (O'Gorman 1976).

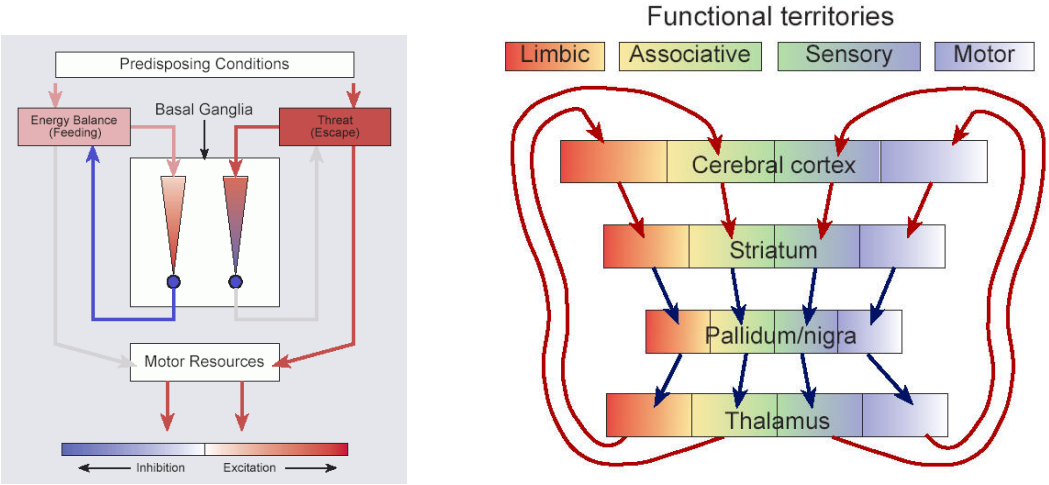
In humans there is considerable evidence for the role of novelty in salience. Novelty may be itself intrinsically rewarding, or provide a 'bonus' in the search for rewards (Kakade & Dayan, 2002). Novelty boosts reward representations in the midbrain and enhances memory formation directly (Schott et al., 2004) and with anticipation (Wittmann, Bunzeck, Dolan, & D uzel, 2007), via recurrent dopaminergic hippocampal-VTA loops (Lisman & Grace, 2005). In the absence of reward, novel stimuli activate the human dopaminergic midbrain more than other candidate forms of salience such as 'rareness' or 'targetness' (Bunzeck & Duzel, 2006).

Similarly the experience and recognition of emotion in humans is highly salient, and experiences of salient stimuli are usually affectively valenced. A capacity for both emotional experience and emotional recognition is evident in humans throughout the lifespan and is central to intra- and interpersonal human experience (Carstensen & Turk-Charles, 1994). Like novelty, emotion captures attention and behaviour, enhances memory and interacts neutrally with the processing of reward in dopaminergic areas (Wittmann, Schiltz, Boehler, & D uzel, 2008). At a neural level, presynaptic dopamine activity both in the amygdala (Kienast et al., 2008) and in the midbrain (Jabbi et al., 2012) modulates the processing of emotional stimuli in the amygdala and its connection with the anterior cingulate cortex (Kienast et al., 2008). From both 'brain-level' and 'mind-level' perspectives, the experience of salience, and therefore of aberrant salience, incorporates dimensions other than just reward, in particular novelty and emotion.

1.2.6 Salience Integration

So what exactly is 'salience', and how do you measure it? Salient stimuli are those that *pull* cognition – including attention, orientation, sensory processing and higher processing – and

push behaviour – response selection, motor planning monitoring and execution. A mechanism for choosing which stimuli to notice and respond to would have to involve all these elements and be able to compare different types of stimuli inputs to coordinate central output processes from attention through to action. Such a mechanism would be phylogenetically old, widely cortically and subcortically connected, and modulated by signals relevant to learning and context. Redgrave and colleagues consider this sorting and prioritising of a vast number of environmental perceptual inputs to restricted cognitive resources a 'Selection Problem' (Prescott, Montes González, Gurney, Humphries, & Redgrave, 2006), and locate the mechanism for its solution in the multiply connected basal ganglia (Redgrave, Prescott, & Gurney, 1999), operating within functionally segregated, parallel, re-entrant cortico-striato-nigro-thalamo-cortical loops (Alexander, DeLong, & Strick, 1986). Such loops are topographically represented according to inputs, outputs and function which include emotional, cognitive and sensorimotor domains (figure 5.2B).



A B

Figure 1.6A A simple instance of a selection problem in a rodent: basal ganglia compute competing inputs to allocate motor resources to ensure survival, dependent on context.(Figure from Prescott et al., 2006). B. Functionally segregated parallel loops maintain cortical representations but facilitate modulatory crosstalk and feedback at each level.

According to this model, competition occurs between stimuli represented through such loops to facilitate allocation of attentional and behavioural resources, in a 'winner takes all' computation. Competition is on the basis of their relative saliency to the organism in the context; *salience* is therefore the common currency used in this competition, the selection criteria for determining which stimuli 'win' (Redgrave et al., 1999). This process may also therefore best fit with what is termed broadly thought as 'salience processing'.

How to best measure this behaviourally and neurally in humans is not easily established. In most experimental tasks a contrast is made on a single dimension between salient and non-salient variants, be they reward predicting, aversion, emotional, reward prediction error, on fMRI activation in a region of interest.

1.2.7 Studies of Aberrant salience in psychosis

Investigations of salience processing in subjects with psychosis have largely focussed on reward related dimensions of salience, reflecting the known role of dopamine in reward related processing. Many of these studies have utilised paradigms based on classical conditioning such as the Monetary Incentive Delay (MID) task (table 1.1). In these paradigms, subjects with psychosis demonstrate relatively reduced behavioural and Blood Oxygenation Level Dependent (BOLD) activation responses to unexpected rewards, reward predicting stimuli or reward prediction errors, and/or relatively increased responses to neutral stimuli. These alterations in neural response can be interpreted as reflecting aberrant salience processing, as predicted by the model (Kapur, 2003).

Studies of salience processing and related concepts are summarised in table 1.1. Surprisingly, given the particular link between the aberrant salience model and delusions and hallucinations, abnormalities on these tasks in patients have often been found to correlate with negative rather than positive psychotic symptoms. Most of these studies neither focus on nor differentiate perceptual, novelty or emotional salience from reward salience.

A recent paradigm, the Salience Attribution Task is notable in that it sets out to differentiate adaptive from aberrant salience, using a probabilistic reward learning game (Roiser et al., 2009). Participants' ratings of reward-relevant and reward-irrelevant stimulus dimensions are linked to adaptive and aberrant salience, respectively. Using fMRI these were differentiated in controls by activation in the DLPFC and middle temporal gyrus (Roiser, Stephan, Ouden, Friston, & Joyce, 2010). Amongst participants with schizophrenia, those with delusions showed reduced adaptive salience and increased aberrant salience to controls (Roiser et al., 2009), in line with the aberrant salience model. The task is currently being applied using fMRI in participants with schizophrenia and in ARMS participants (Roiser, personal communication).

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fMRI Studies of Salience Processing in Psychosis

Author	Year	Salience Dimension	Brain regions analyzed	SCZ	Diagnosis	Illness stage	Medication	HC	Task	Main findings
Juckel	2006	Reward	ROI	20	DSM-scz	Chronic	A	10	Monetary incentive delay	Blunting of VS activation to reward predicting cues not observed in patients treated with atypical vs typical neuroleptics
Schlagenhauf	2008	Reward	ROI	20	DSM-scz	Chronic	A	10	Monetary incentive delay	Failure to activate the VS to reward predicting cues is pharmacologically state-dependent
Juckel	2006	Reward	Whole + ROI	10	DSM-scz	First-episode	7DN, 3DF	10	Monetary incentive delay	Reduced activation in the VS to reward predicting cues is correlated with the severity of negative symptoms in medication-free patients
Corlett	2007	Prediction Error (PE)	ROI	12	DSM-scz(a)	First-episode	8A, 4DF	12	Associative causal learning task	The extent of disrupted prefrontal prediction-error processing is significantly related to delusion formation
Jensen	2008	Aversion	Whole + ROI	13	DSM-scz	Chronic	A	13	Aversive Pavlovian learning task	Increased activation in the VS to neutral cues (CS-) in an aversive conditioning paradigm.
Murray	2008	Reward PE	Whole + ROI	13	DSM-scz(a)	First-episode	5DN, 8A	12	Monetary gains	Reduced responses to reward prediction error in the midbrain and key target regions in psychosis
Abler	2008	Reward PE	Whole + ROI	12(c)	DSM-scz/scf	Chronic	A	12	Monetary incentive delay	Alterations in the coding of prediction error signals in the VS of manic psychosis vs scz psychosis
Schlagenhauf	2009	Reward	ROI	15	DSM-scz	Mixed	8DN, 7DF	15	Monetary incentive delay	Differential impairment of and reduced VS prefrontal connectivity during processing of reward and loss-avoidance in drug-free patients
Walter	2009	Reward	Whole + ROI	16	DSM-scz	Chronic	A	16	Monetary incentive delay	Patients lack the U-shaped activation curve in the ventrolateral prefrontal cortex during the salience contrast
Waltz	2009	Reward	Whole + ROI	18	DSM-scz	Chronic	A	18	Passive reward conditioning	Patients show attenuated midbrain and striatal responses to a primary reinforcer
Dowd	2010	Emotion	Whole + ROI	40	DSM-	Chronic	A	32	Arousal to	Reduced activation to positive versus negative stimuli

					scz/scf				emotions	in the VS associated with anhedonia in patients
Simon	2010	Reward	Whole + ROI	15	DSM-scz/scf	Chronic	A	15	Monetary incentive delay	VS activation during reward anticipation was negatively correlated with apathy, during receipt was negatively correlated with severity of depressive symptoms
Koch	2010	Learning	Whole + ROI	19	DSM-scz	Chronic	A	20	Trial-and-error learning task	Reinforcement-associated processing and reinforcement learning is impaired in patients
Romaniuk	2010	Aversion	Whole + ROI	20	DSM-scz/scf	Chronic	A	20	Aversive Pavlovian conditioning	Inappropriate activation of the midbrain to CS- during conditioning is associated with the severity of delusional symptoms
Waltz	2010	Reward	Whole + ROI	17	DSM-scz	Chronic	A	17	Monetary incentive delay	Systematic relationships between clinical symptoms and neural responses to stimuli associated with rewards and punishments
Harvey	2010	Emotion	Whole + ROI	30	DSM-scz	Chronic	27A, 3DF	26	Arousal to emotions	Anhedonia severity is linked to a poor modulation of emotional regions during the hedonic processing
Gradin	2011	Reward	Whole + ROI	15(b)	DSM-scz	Chronic	A	20	Rewarding learning task	In patients reduced prediction error signals correlated with severity of negative psychotic symptoms
Diaconescu	2011	Reward	Whole + ROI	13	DSM-scz	Chronic	A	13	Appetitive conditioning	Patients failed to show GSR differences between CS+ and CS−. Altered effective connectivity in response to the CS− in patients
Nielsen	2012	Reward	Whole + ROI	31	ICD-scz/scf	First-episode	DN	31	Monetary incentive delay	Alterations during reward anticipation in schizophrenia in relation to overall salience. In VS these changes were associated with positive symptoms.
Morris	2012	Learning	Whole + ROI	21	DSM-scz/scf	Chronic	A	16	Pavlovian cue-outcome association	Aberrant activity in the VS is the core dysfunction in the neural circuitry used to differentiate expected and unexpected feedback

A, Antipsychotic; DN, Drug Naive; DF, Drug Free; SCZ, Patients with schizophrenia; HC, Health controls, DSM-scz, Schizophrenia DSM diagnosis; DSM/ICD-scz/scf, Schizophrenia or Schizoaffective DSM/ICD diagnosis; fMRI, functional Magnetic Resonance Imaging; GSR, Galvanic Skin Responses; CS+, Conditioned Stimuli; CS- neutral comparators; US, Unconditioned Stimuli; VS, Ventral Striatum; ROI, Region Of Interests analysis; VBM, Voxel Based Morphometry

In this thesis, "novelty salience" means salience relating to detecting whether a stimulus stands out from the background because it seems new; "emotional salience" relates to stimulus prominence related to the detection and experience of emotional arousal and valence; "reward salience" is related to a stimulus' appetitive motivational properties.

There is good evidence to suggest that novelty processing may be awry in psychosis, which often begins with *'an altered sense of novelty and an aberrant assignment of salience…*' (Kapur, Mizrahi, & Li, 2005b) and a misplaced sense of recognition and familiarity (Mishara, 2010). Like reward, the processing of novelty is associated with activation of the substantia nigra/ventral tegmental area (SN/VTA), the origin of dopaminergic neurons that project to the striatum. Their engagement by novelty is evident in dopamine cell recording studies in primates (Schultz, 1998), and in human fMRI studies directly (Bunzeck & Duzel, 2006) and with anticipation (Wittmann et al., 2007) and the interaction of novelty and reward has been demonstrated in healthy subjects (Bunzeck, Doeller, Dolan, & Duzel, 2012). To my knowledge neuroimaging has not yet been used to examine the neural substrate of novelty processing in subjects with psychosis. Thus, there are no studies of novelty salience in Table 1.1.

Abnormalities in emotional perception, experience and expression have been considered core to psychosis since Bleuler (reviewed in Kohler & Martin, 2006). More recently subjects with schizophrenia and those at high risk have shown behavioural and fMRI abnormalities in detecting and processing emotional salience (Holt et al., 2006; L. K. Phillips & Seidman, 2008; Taylor, Phan, Britton, & Liberzon, 2005), and the interaction of reward and emotion processing has also been demonstrated in healthy subjects (Wittmann et al., 2008). Emotional stimuli are processed through a network involving the amygdale where dopamine may 'gate'

processing (Kienast et al., 2008), where dysfunction has been proposed as central to schizophrenia pathophysiology (Aleman & Kahn, 2005), and emotional aspects of psychotic symptoms may be critical in the distress, impairment and help-seeking that results (Freeman & Garety, 2003).

To date, the salience paradigms that have been used to study subjects with psychosis have all focused on a single dimension of salience in isolation, such as reward (Table 1.1). However, the experience of salient stimuli, *pulling* attention and thought towards them, and *pushing* behaviour, is unified yet multifaceted, and usually motivationally and affectively loaded. Analogous to a physical 'saliency map' (Z. Li, 2002), higher elements such as reward, novelty and emotion may interact to help determine the most salient stimuli for the organism in its current state and context. It is therefore be useful to consider how the different elements of salience interact with each other.

1.2.8 The Salience Integration Task

The Salience Integration Task is a novel task designed as part of the present thesis, and is described in detail in chapter 2. It permits experimental manipulation of three elements of salience processing - reward, novelty and emotion – in a visual context, whilst holding basic elements – size, colour, luminance, pixel count - as constant as possible. By using a balanced factorial design it facilitates examination of behavioural and neural responses to each element in isolation, as well as in interaction. Reaction time is used to index altered motor responses to salient elements; a delayed recognition task examines the impact of these on memory. The task is performed whilst fMRI scanning is performed in order to visualise the neurofunctional correlates of integrated salience processing.

1.3 Dopamine in psychosis

1.3.1 Dopamine pathways

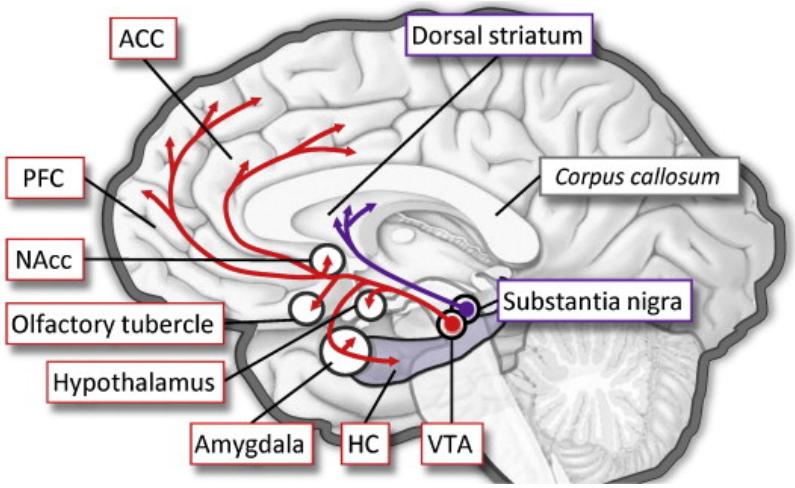

Figure1.5 Dopaminergic mesolimbic (red) and nigrostriatal (purple) pathways project from the midbrain to a range of limbic, striatal and prefrontal targets. NAcc: Nucleus Accumbens, PFC Prefrontal Cortex, ACC Anterior cingulate cortex, HC Hippocampus, VTA Ventral Tegmental Area. Figure adapted from (Perogamvros & Schwartz, 2012)

Dopamine neurons, relatively few in number, originate in a small area of the ventral mesencephalon and innervate basal ganglia (particularly the striatum), limbic regions (amygdala and hippocampus) and forebrain (particularly orbitofrontal and anterior cingulate). These dopamine neurons function in motor control, executive, motivational and emotional processes, and when impaired lead to a range of neurological and psychiatric disorders.

1.3.2 Studies of Dopamine in psychosis

Several lines of evidence support the role of dopamine in psychosis, which originated from the discovery of the mechanisms of antipsychotics in altering dopamine metabolism (Carlsson & Lindqvist, 1963), and the observation that the antihypertensive drug Reserpine, which

blocks dopamine uptake into presynaptic vesicles, could relieve psychotic symptoms (Schroeder & Perry, 1955). Subsequent work has demonstrated other psychotogenic compounds such as amphetamine are dopamimetic, and all effective antipsychotics are dompamine blockers (Kapur & Mamo, 2003). Direct evidence comes from insights of neurochemical brain imaging.

There have now been over fifty studies using in vivo molecular imaging techniques to probe pre-synaptic and post-synaptic aspects of striatal dopamine neurotransmission in patients with psychotic disorders. These cover presynaptic synthesis capacity, dopamine receptor availability, baseline occupancy and dopamine release (Howes et al., 2007).

The first step, dopamine synthesis capacity, can be measured using radiolabelled-3,4-*l*-dihydroxyphenylalanine (L-DOPA). Studies using this technique have found elevated dopamine synthesis capacity in schizophrenia; recent meta-analyses indicate the overall elevation is around 14% and large in effect size (Fusar-poli & Meyer-Lindenberg, 2012a; Howes et al., 2012).

The next step is the release of dopamine into the synapse, indexed by measuring the change in radiotracer binding following a challenge known to alter dopamine neurotransmission (Laruelle et al., 1997). In such studies in subjects with schizophrenia radiotracer displacement following amphetamine has consistently been found to be greater than that in controls, and related to the worsening of psychotic symptoms induced by amphetamine (Abi-Dargham et al., 1998; Laruelle, Abi-Dargham, Gil, Kegeles, & Innis, 1999). This is also evident in similar studies using a psychosocial stress challenge (Mizrahi, Addington, Rusjan, & Suridjan, 2011). Interestingly this elevation appears to be a psychotic state phenomenon, and much less marked in stable remitted patients (Laruelle et al., 1999). Resting synaptic dopamine activity

is assessed by depleting presynaptic dopamine stores using a drug such as alpha-methyl-*para*-tyrosine, which blocks dopamine synthesis and reduces extracellular dopamine levels. Studies using this technique have found that baseline occupancy of D2/3 receptors by dopamine is elevated in schizophrenia, which suggests that extracellular dopamine concentrations are elevated at baseline (Abi-Dargham et al., 2000).

In contrast findings on D2/3 receptor availability have been less consistent. Meta-analysis of the studies to date indicates that D2/3 receptor availability is elevated in schizophrenia, but the effect size is small (Howes et al., 2012). Dopaminergic transmission in the striatum is predominantly terminated reuptake into the nerve terminals by dopamine transporters. As meta-analyses of the studies of dopamine transporter availability indicates that this is unaltered in schizophrenia, there does not seem to be a compensatory increase in the capacity of the dopamine system to 'buffer' the effects of disordered dopamine neurotransmission in schizophrenia (Fusar-poli & Meyer-Lindenberg, 2012b).

Studies to date have focussed on striatal dopaminergic neurotransmission (Howes et al., 2007). Consequently it remains to be determined how this reflects dopamine function in other regions, although meta-analysis of findings on D2/3 receptor availability outside of the striatum indicates that this aspect of dopamine neurotransmission is unaltered in schizophrenia (Kambeitz & Howes, 2012). Nevertheless, taken together, molecular imaging studies provide compelling evidence that striatal dopaminergic neurotransmission is altered in schizophrenia, and linked to the onset of psychosis.

1.3.3 Studies in Ultra High Risk samples for psychosis

Elevated dopamine synthesis capacity and stress induced dopamine release has also been found in high risk subjects experiencing prodromal symptoms, prior to the onset of the full-blown illness (Howes et al., 2009). Such elevations appear to be particularly marked in the subgroup that go on to transition to psychosis (Howes, Bose, Turkheimer, Valli, Egerton, Valmaggia, et al., 2011a), and longitudinal PET studies in these subjects indicate that dopamine synthesis capacity increases further with the onset of psychosis (Howes, Bose, Turkheimer, Valli, Egerton, Stahl, et al., 2011b).

1.4 Circuit models of dopamine dysregulation in psychosis

1.4.1 Overview

While there is increasing evidence of altered dopamine function in psychosis, the cause of this is not well understood. Early accounts focussed on those dopamine neurons that innervated subcortical regions, which were overstimulated by excessive dopamine transmission, and blocked by antipsychotics (Seeman & Lee, 1975). Dopamine projections to the cortex were then discovered, and shown to have reciprocal regulation to that of striatal dopamine (Pycock, Kerwin, & Carter, 1980). It was suggested that reduced prefrontal dopamine may underlie negative symptoms in schizophrenia, and causally relate to exaggerated striatal dopamine (Davis:1991tk Meyer-Lindenberg et al., 2002). However direct human evidence of frontal hypodopaminergia was limited, and beyond simple 'hyper' or 'hypo' dopaminergia there was no understanding of exactly how or where dopamine dysregulation occurred in the brain or

related to symptoms. Advancing this position entails a more detailed understanding of the regulation of dopamine firing but studying brain circuitry in detail in humans in vivo is difficult.

1.4.2 Animal Models of Schizophrenia

Reliable animal models are therefore valuable preclinical tools with which to develop such an understanding (Jones 2011). However modelling and assessing the often uniquely human traits of psychiatric disorders is difficult. Models of disorders such as schizophrenia fall into four main categories of induction - developmental, drug-induced, lesion or genetic manipulation (table 1.2). Most display some aspects of the behavioural and physical phenotype of the positive symptoms of schizophrenia, but a limited number, including the developmental methylazoxymethanol (MAM) and neonatal hippocampal lesion models, also show behavioural and neurobiological aspects related to negative and cognitive symptom domains (Jones 2011).

Animal models provide a neurofunctional context to test human models of disease. The characteristics of several major animal models of psychosis against key features are summarised in table 1.2.

Major Animal Models of Schizophrenia

Animal Model	Basal & drug induced locomotor activity	Sensorimotor gating	Social interaction	Cognition	Structure/Neurochemistry
Amphetamine models	Sensitization of locomotor response to amphetamine	Persistent PPI deficit	No reduction	Attention and set shifting deficit, no episodic memory problems	Enhanced mesolimbic DA response; altered ACh function in PFC
PCP models	Sensitization of locomotor response to amphetamine, PCP and mild stress	No PPI deficit	Reduced frequency/duration of primate social behaviour	Set shifting and novel recognition impaired, impaired T-maze performance	Reduced basal and stress induced PFC DA and glutamate, decreased synaptic spines on PFC neurons and cortical and hippocampal parvalbumin positive neurons
DISC-1 knockout mutants	Hyperactivity in some but not all	PPI deficits in some but not all mutants	Reductions seen in some	Impaired T-maze performance, impaired spatial WM performance in some	Reduced brain volume, enlarged LV in most. Reduced hippocampal and PFC dendritic density/structure and parvalbumin in some
Neuregulin 1 /ErbB4 knockout mutants	Increased spontaneous locomotor activity, inconsistent stimulant response	PPI deficits in most	Deficits in social interaction and responses to novelty, increased aggression	Impaired contextual fear and MMN in some	Increased lateral ventricles and reduced hippocampal spine density; reduction in functional forebrain NMDA receptors
Dysbindin knock-out mutants	Spontaneous locomotor hyperactivity and hyper-responsivity to amphetamine	*Increased* PPI and startle response	Reduced social contact	*Improved* T-maze task performance ; impaired spatial reference memory /novel object recognition	Hyperexcitability of PFC pyramidal neurones; altered synaptic structure and formation; elevated HVA/DA ratio in cortico-limbic regions
Reelin knock-out mutants	*Reduced* spontaneous locomotion; enhanced amphetamine response	Variable PPI responses	Some reduction of social activity	Some learning deficits in acquisition of operant tasks normal reversal learning, inhibitory control, and water maze task	*Increased* neuronal packing and decreased dendritic spine density in PFc and hippocampal neurones

Post-weaning social isolation	Hyperactivity in a novel arena 2–3 weeks after isolation; hyper-responsivity to amphetamine with increased DA release	Persistent, but strain-dependent reduction in PPI appearing about 6 weeks after isolation	Increased aggression and *increase* in total social interaction	Deficit in novel object recognition;	Reduced PFC volume; reduced dendritic spine density, cytoskeletal alteration and loss of parvalbumin-containing interneurones and reelin in the hippocampus; reduced PFC D1 binding, increased spontaneously active VTA DA neurones
Neonatal ventral hippocampal lesion	Locomotor hyper-responsivity to stress, amphetamine and NMDA receptor antagonists	Adult onset deficit in PPI	Deficits in social interaction with increased aggression at all developmental ages	Impaired acquisition of T-maze; deficit in extra-dimensional shift and reversal in the attentional set-shifting task	Unaltered basal nAcc DA release, but enhanced response to stress or amphetamine; reduced mPFc NAA levels and GAD67 mRNA expression
Gestational MAM (GD17)	Spontaneous hyperactivity in novel arena emerging at puberty. Enhanced amphetamine- and NMDA antagonist-induced locomotion.	Puberty onset deficit in PPI	Reduced total social interaction appears prior to puberty.	Normal acquisition, but impaired re-learning in the Morris water maze; impaired extra-dimensional shift in attentional set-shifting task	Reduced PFC and hippocampal size, enlarged ventricles, reduced hippocampal soma size and neuropil; enhanced nAcc DA release; spontaneously hyperactive VTA DA neurones; decreased PFC parvalbumin GABA interneurons

Table 1.2 - Comparative overview of features of selected animal models of schizophrenia- adapted from Jones et al 2011

1.4.3 The Gestational MAM model

Of all of the animal models of schizophrenia illustrated in Table 1.2, the one that has perhaps the most features consistent with those of human schizophrenia is the Gestational MAM model. Methylazoxymethanol (MAM) is a naturally occurring anti-mitotic DNA methylating agent that targets neuroblast proliferation in the CNS (Moore, Jentsch, Ghajarnia, & Geyer, 2006). Administration of MAM to pregnant rat dams therefore affects brain structures in the developing foetus that are developing most rapidly, and are highly timing dependent (Balduini, Lombardelli, Peruzzi, & Cattabeni, 1991). Administration at Gestational Day (GD) 15 leads to gross morphological brain changes, including microcephaly and profound cortical dysplasias. At GD17 however, MAM administration leads to a restricted and preferential size reduction in PFC and limbic structures, especially a specific reduction in neuronal number in the CA2 subfield of the hippocampus, and reduced soma size and neuropil in other hippocampal subfields. There are specific cortical thickness reductions in the hippocampus, thalamus and several other regions, and a reduction in total brain weight of around 11% (reviewed in Lodge & Grace, 2009). Many of the behavioural changes seen in GD17 MAM rats emerge during puberty, as in schizophrenia (Le Pen, Gourevitch, Hazane, Hoareau, & Jay, 2006). These include reductions in spontaneous and social activity, increased locomotor activity to a novel arena and enhanced locomotor responses to amphetamine. Alongside this are increased dopamine release to amphetamine challenge in the nucleus accumbens, but not in the frontal cortex (Flagstad et al., 2004) and enhanced sensitivity to the NMDA antagonist MK-801 which causes greater hyperactivity in MAM rats than in controls (Le Pen, Jay, & Krebs, 2011). Deficits in sensory gating, which indexes pre-attentive sensory filtering, also emerge in puberty in MAM rats (Moore et al., 2006).

Electrophysiological work in MAM rats has demonstrated increases in the number of spontaneously active dopaminergic neurons in the Ventral Tegmental Area (VTA) of the midbrain. This work relates to the distinction between between tonic and phasic regulation of dopamine outflow (Grace, 1991). Dopamine neuron activity states are regulated in the rodent by the ventral subiculum of the hippocampus and the pedunculopontine tegmentum. Stimuli that are behaviorally salient activate the pedunculopontine tegmentum (PPTg) causing glutamate release onto mesolimbic dopamine neurons and leading them to burst fire. The total amplitude of this phasic dopamine signal is dependent on the number of dopamine neurons that the PPTg can activate, since it can only cause burst firing in those dopamine neurons that are already spontaneously firing - inactive neurons' glutamatergic NMDA receptors are blocked by Mg^{2+}. By controlling the population activity (i.e., proportion of dopamine neurons firing spontaneously), the ventral subiculum regulates the 'gain' of the phasic signal, which in health facilitates adaptation of total dopamine output according to context. In a safe and well-known environment this gain is set at a low level (figure 1.6A). Novel salient stimuli activate the PPTg but the total response amplitude is low, garnering little attention or behavioural activation. In a novel, dangerous or potentially rewarding environment the gain is set to high (figure 1.6B), and lower level salient inputs lead to larger amplitude dopamine output and greater attentional and behavioural activation. Grace hypothesises that in the context of states such as schizophrenia, chronic stress or with psychostimulant use the ventral subiculum is overactive and maintaining nearly all of the dopamine neurons in an active state. In this situation, minimally salient or even non-salient stimuli lead to large dopamine outputs, causing the experience of heightened vividness, alertness and significance experienced by subjects in psychotic states (figure 1.6C).

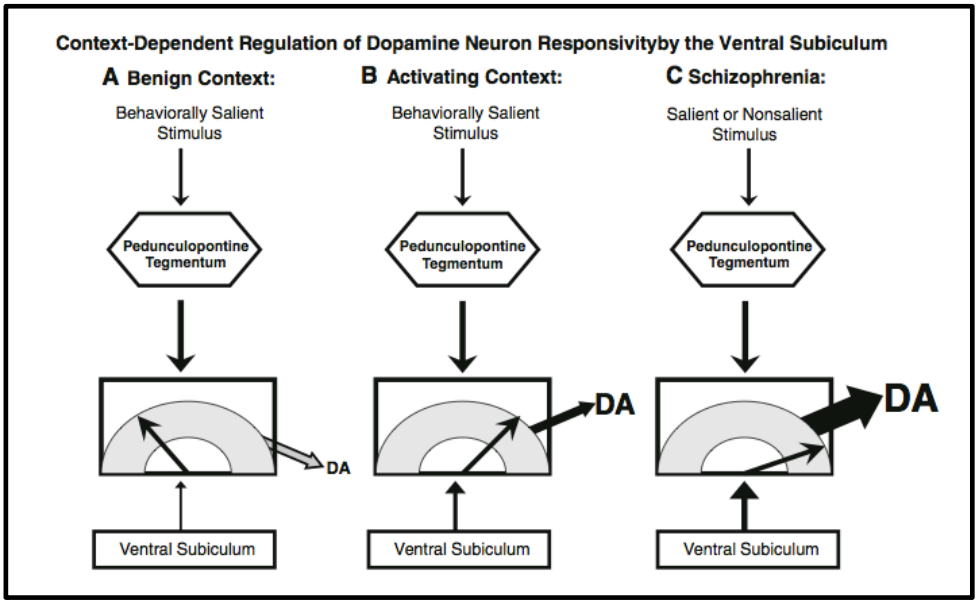

Figure 1.6 Contextual information provided by the hippocampus regulates gain of phasic dopamine responses to salient stimuli. In dangerous novel or rewarding contexts smaller simuli lead to greater output. In schizophrenia all stimuli lead to laximal output – figure adapted from Grace 2011.

In this model contextual information is provided by descending inputs from the ventral subiculum. This hippocampal outflow area generates novelty signals based on perceptual inputs against predictions arising from stored information (figure 1.7, Lisman and Grace 2005). This signal passes through the accumbens to incorporate information about motivational relevance of a context, such as reward status or goal relevance. Emotional information from limbic areas such as the amygdala and other relevant aspects of salient stimuli within this context input on the PPTg leading to glutamatergic activation of dopamine neurons (figure 1.7). Dopamine output is to main projection areas such as the striatum and prefrontal cortex and also recurrent pathways to the hippocampus where it is thought that dopamine enables modification of Long Term Plasticity (LTP) and enhanced memory

formation for salient stimuli and contexts (Grace, Floresco, Goto, & Lodge, 2007; Lisman & Grace, 2005) .

This elegant model provides a clear anatomical framework for the integrated processing of Reward Novelty and Emotional dimensions of salience, with key regions including the hippocampus, striatum, amygdala and midbrain.

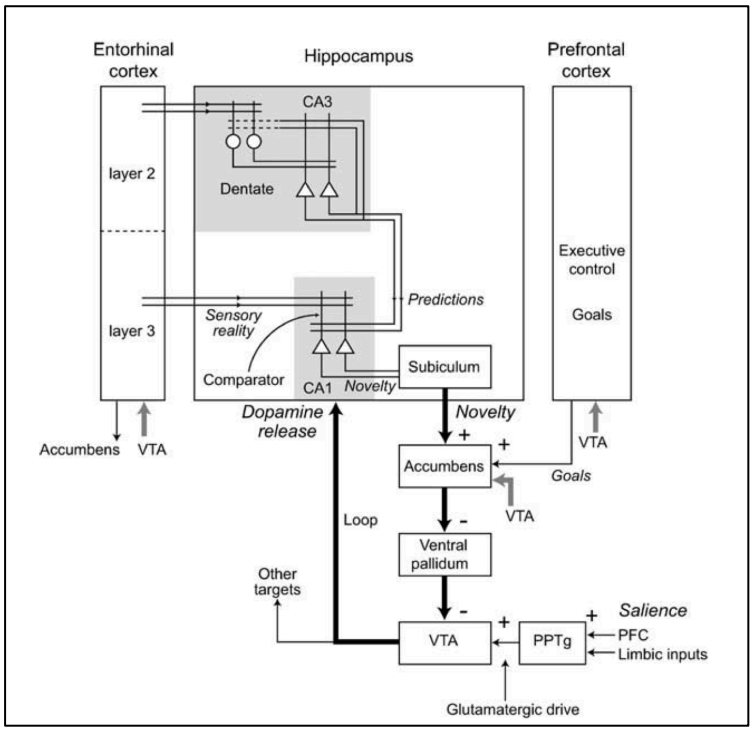

Figure 1.7 VTA output is driven by ventral hippocampal outflow and other limbic and PFC inputs. Figure from Lisman and Grace 2005

VTA dopamine neuron hyperactivity recorded in MAM rats can be reversed by inactivation of the ventral hippocampus (Lodge and Grace 2007). This is true also of amphetamine induced hyperlocomotion. Grace and colleagues suggest therefore that in MAM rats, and by extension in schizophrenia, overactivity in the ventral hippocampus drives hyperactivity of VTA neurons by upregulating the gain of the system and increasing total mesolimbic

dopamine output, resulting in positive psychotic symptoms. They suggest that this hippocampal overactivity is particularly located in the ventral subiculum, or outflow area, of the hippocampus (figure 1.7), and may be the consequence of MAM causing a loss of parvalbumin-containing GABAergic interneurons in this area (Penschuck, Flagstad, Didriksen, Leist, & Michael-Titus, 2006). This is consistent with models of interneuron dysfunction (Olney et al., 1999) and multiple lines of evidence of hippocampal dysfunction in schizophrenia (Tamminga, Stan, & Wagner, 2010). In both MAM treated rats, and possibly also in human subjects with schizophrenia, loss of parvalbumin-GABAergic regulation of hippocampal activity leads to hyper-responsivity of the DA system and loss of control over appropriate responses to stimuli.

1.4.4 The Hippocampus in psychosis

Grace and colleagues' proposal of hippocampal overactivity underlying dopamine dysregulation chimes with converging evidence implicating of alterations in hippocampal structure and function in psychosis (Small, Schobel, Buxton, Witter, & Barnes, 2011; Tamminga et al., 2010). It a also site of action of environmental factors related to the onset and relapse of psychosis, including psychoactive substances such as cannabis (Arseneault, Cannon, Witton, & Murray, 2004; Yücel et al., 2008), and psychosocial stress (L. J. Phillips et al., 2006). Failure of the prefrontal cortex and ACC to regulate amygdalar responses may render the hippocampus vulnerable to sustained stress (Lodge & Grace, 2011). Both structural and functional changes in the hippocampus have been demonstrated in schizophrenia and in subjects with an ARMS (Palaniyappan, Balain, & Liddle, 2012; Tamminga et al., 2010; Wood, Kennedy, Phillips, & Seal, 2010). There is also recent direct evidence of hippocampal overactivity in vivo. Schobel and colleagues used high resolution contrast MRI to

demonstrate increased blood flow in the CA1 subfield in subjects with schizophrenia, and also in those with prodromal signs of psychosis, that predicted subsequent transition to psychosis (Schobel 2009).

While the dorsal hippocampus (analogous to the posterior hippocampus in humans) has a known role in spatial context, more ventral (anterior) portions connect more extensively limbic structure and add 'affective layering' to location - signifying the 'emotional significance' of place (Grace 2011). Thus the ventral hippocampus is involved in context dependent fear conditioning and is well placed to regulate dopaminergic tone output sensitive to context.

1.5 Aims and predictions of this thesis

In the sections above I have described two key models informing a CNP based account of the development of psychotic symptoms. The first stages of the aberrant salience model of psychosis (figure1.1 Kapur, 2003) predict that dopamine dysfunction leads to altered salience processing and the phenomena of delusional mood, or 'Trema' (Mishara, 2010) preceding the formation of clear psychotic symptoms. Healthy salience processing includes dimensions of novelty, reward and emotion that are integrated to scale context-appropriate dopaminergic signals to behaviourally salient stimuli. In MAM treated animals, ventral hippocampal overdrive dysregulates the context dependent control of dopamine gain. However, the extent to which these models are applicable in humans remains to be addressed. Three key aims therefore proceed:

1.5.1 A framework of integrated salience processing

The aberrant salience model of psychosis, whilst providing good face and construct validity, does not specify which dimensions of salience processing are altered. This follows an absence of a clear framework for understanding the contribution and interaction of various elements of healthy salience processing. Thus, to date, research on altered salience processing in psychosis has largely been limited to reward based tasks. As described, there is reason from both neurobiological and phenomenological perspectives to consider additional features of salience, in particular the role of novelty and emotion. Developing such a framework using behavioural and functional brain imaging data will be the focus of the first part of this study.

1.5.2 Dimensions of altered salience processing in subjects at Ultra High Risk for psychosis

Applying such a framework for salience processing to subjects with attenuated symptoms of psychosis is the second major focus of this study. According to the aberrant salience model, individuals in the prodrome of psychosis experience alterations in the salience processing, leading to the formation of psychotic symptoms. This group are also particularly suitable for studies in this area as they are usually medication naïve, and thus free from the confounding effects of antipsychotic treatment, which may be critical given the key role of dopamine in salience processing. Understanding altered salience processing in these subjects may thus help to reveal the mechanisms driving the initial formation of psychotic symptoms.

1.5.3 The neurochemical basis of normal and abnormal salience

The final focus of this work will be to understand the neurochemical basis of normal and abnormal salience processing and test the predictions of the MAM model, that ventral

hippocampal output regulates context dependent midbrain dopamine responses to salient stimuli. I will employ PET scanning in combination with functional MRI to test the relationship of hippocampal activation to salient stimuli with dopamine synthesis capacity measured in the striatum. Insights gained will be related to the search for new avenues for treatment and prevention.

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2. A Framework for Salience Processing in Healthy Individuals

2.1 Introduction

Models of alterations in 'salience' processing in psychosis and other psychiatric illness (Dunlop & Nemeroff, 2007; Heinz, 2002; Kapur, 2003) do not often agree on the cognitive processes involved in normal salience processing, or which elements of salient stimuli are critical; empiric testing of such models tends to rely on a single dimension of salience. For aberrant salience models of psychosis this has largely been that of reward, extending from the customary association of dopamine with reward processing (Dunlop & Nemeroff, 2007; Heinz, 2002; Kapur, 2003; Schultz, 1997), and the known role of dopamine in psychosis (Fusar-Poli, Howes, T, Ungless, & Kapur, n.d.; Heinz & Schlagenhauf, 2010).

In contrast the experience of salience is multifaceted, as are salient stimuli. In addition to basic 'physical' elements such as colour contrast and movement (Nothdurft, 2000; Wolfe, Wolfe, Horowitz, & Horowitz, 2004), salient stimuli can have elements of novelty, reward or threat and affective valence and arousal (Schultz, 2010). The experiential phenomenon of 'salience', that draws attention, orientation and behaviour, may emerge from interactions between such stimulus dimensions (e.g. 'saliency maps' in vision Li, 2002) with both state and trait aspects of the organism. In testing disease models invoking an alteration in salience processing it is important to have a clear reference framework of normal processing that addresses such multidimensionality and its integration. This chapter describes the application of a novel behavioural and fMRI task aimed at advancing such a framework in a group of healthy participants.

2.2 The Salience Integration Task

The Salience Integration Task (SIT) is a novel modification of a standard Monetary Incentive Delay task (Knutson, Adams, Fong, & Hommer, 2001; Krebs, Schott, & Duzel, 2009a; Wittmann, Schiltz, Boehler, & D uzel, 2008) and was designed to study novelty, emotion and reward salience and their interaction. 'Salience' was defined as the extent of behavioural and neurofunctional modification a stimulus provoked. Behaviour was measured in terms of reaction time and delayed recognition. Neural function was measured in terms of BOLD related fMRI activation in a predefined network of brain structures of interest taken from a key animal model (see section 1.4.1).

All three salience dimensions were inherent to the picture cue. At the beginning of each trial, the indoor-outdoor setting of visual picture cues indicated whether the current trial held the chance for a 20-pence reward (reward-predicting cues, 80% of indoor scenes), or had no incentive relevance (neutral cues, 80% of outdoor scenes). Having the reward relevant dimension (indoor-outdoor) implicit in the cue, rather than preceding it or remaining separate, distinguished the from some other variations of the MID (e.g. Wittmann et al., 2008). Half of the cues were indoor scenes and half were outdoor.

To generate the novelty dimension, 50% of both reward-predicting and neutral cues were also familiarized beforehand (see pre-familiarization procedure section 2.2.2), leaving 50% as novel images. Furthermore 50% of all of the pictures (indoor and outdoor, familiar and novel) were also emotionally arousing pictures taken from the International Affective Picture System (Lang & Bradley, 1998). The IAPS is a standardised set of pictures with reference valence and arousal data for a wide range of reference participants' emotional responses. Indexing emotional responses along dual bipolar dimensions generates a simple circumplex model of affect (figure 2.1).

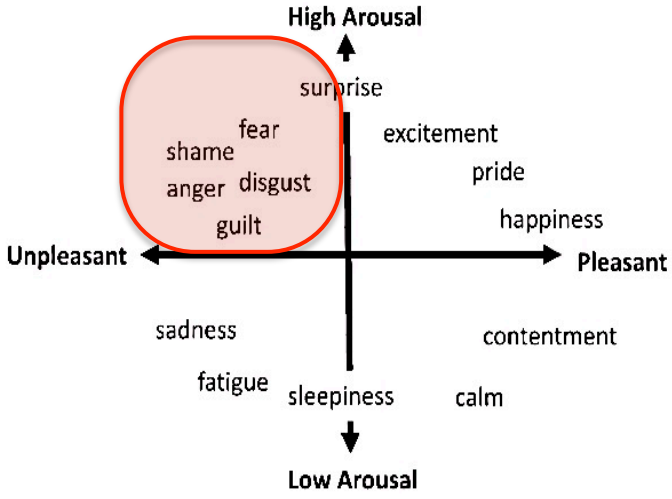


Figure 2.1 Dimensions of arousal and valence used in IAPS pictures. Scenes for the SIT were negatively valenced with a minimum arousal level of 3 (normal range 0-8) - top left quadrant (Lang & Bradley, 1998) .

As positively valenced pictures may generate a rewarding 'liking' responses (Berridge, 1998), in order to keep emotional and reward dimensions orthogonal I used negative valenced pictures only, with a minimum arousal level of 3.0 (mean (SD) arousal= 5.6 (0.86) Lang & Bradley, 1998). There were no significant differences in arousal levels across SIT categories or new distractor pictures used in the recognition tasks (figure 2.2).

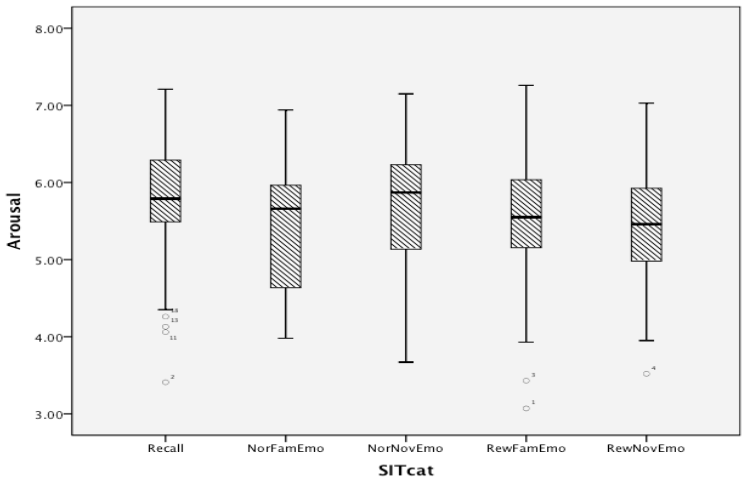


Figure 2.2 - IAPS Arousal levels for each Emotional SIT category and New distractor pictures in recognition tasks. SITcat: SIT category; Recall: new distractor pictures, NorFamEmo: Non-rewarding, familiar, emotional pictures; NorNovEmo: Non-rewarding, novel, emotional pictures; RewFamEmo: Rewarding Familiar, Emotional pictures; RewNovEmo: Rewarding, Novel, Emotional pictures.

All pictures were carefully prepared in order to minimise response differences due to physically salient visual characteristics. All pictures were converted to greyscale and normalised to a mean grey level of 125 (SD 70), resized to 500 x 300 pixels and presented on a grey background. Following processing all pictures were checked to ensure they remained easily identifiable as indoor or outdoor, and in the case of the IAPS pictures remained readily evocative. Participants also rated the emotional arousal level of each picture after scanning. Trials were presented in a randomised order.

This resulted in a 2x2x2 factorial event-related design, in which the cue variables novelty, negative-emotionality and reward-prediction were manipulated separately, yielding 8 experimental conditions that were used to form contrasts in the subsequent behavioural and fMRI analyses of main effects and interactions (figure 2.3). Except where specified, the SIT category of Reward refers to the category of reward-predicting pictures (Indoor scenes), and the SIT category of Emotion refers to negative-emotion evocation by IAPS scenes.

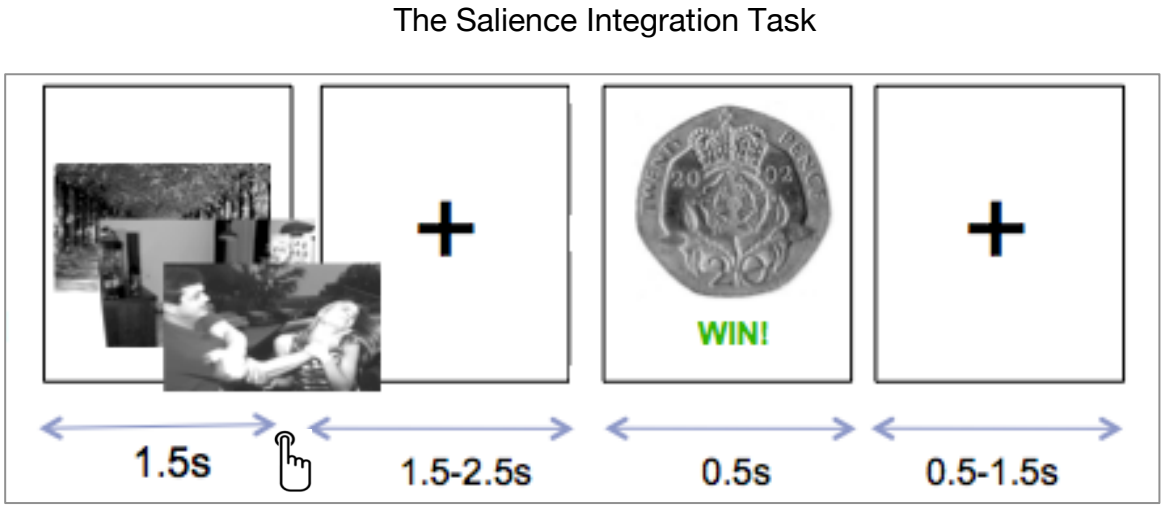


Figure 2.3 - SIT task : Visual picture cues varied along 3 dimensions: Reward prediction (Indoor-outdoor), Novelty and Emotion. Following each cue participants pressed a button, followed by a fixation cross and then either a money reward or no reward outcome. 2 'NoGo' trials served as an attentional control, where participants were instructed to withhold the button press.

Following presentation of the picture cue for 1500ms, participants were instructed to press a button with their dominant hand index finger, regardless of cue type, aside from 2 pre-assigned and randomly inserted 'No-Go' pictures (1 indoor, 1 outdoor).

These 'No-Go' pictures served as attentional controls and encouraged processing of scene detail and incidental memory encoding; participants were not informed that there would be a later memory test. After the picture cue, a black fixation cross on a grey background followed for 1000ms-2500ms, followed in rewarded trials by picture of a 20p coin with 'WIN!' in green text underneath, or in unrewarded trials a similar shaped blank icon with the words 'No Money Available' in red text for 750ms, followed by a further fixation cross for 150ms-1650ms (figure 2.3)**.** Participants were told to respond quickly and accurately for each trial, although reward contingencies were predetermined for each trial to provide a fixed reinforcement ratio (0.8). There were 35 trials in each of the 8 response categories and 35 No-Go trials giving a total of 315 trials. The inter-trial interval was 4.9s giving a total paradigm length of 25min 43.5s.

After performing the SIT in the scanner, participants performed two recognition tasks for the picture cues, at 1hr and 24hrs. This was in order to test both encoding and consolidation of recognition, which may require different physiological processes (Frey & Morris, 1997), the latter being more dopamine dependent (Lisman, Grace, & Duzel, 2011). During this test participants also judged the confidence of their recognition memory according to the Remember/Know procedure (Duzel, Tulving, Yonelinas, Mangun, & Heinze, 1997; Wheeler, Stuss, & Tulving, 1997) and rated each picture according to its emotional arousal level using a visual analogue scale.

2.3 Hypotheses

1. Reward prediction, novelty and aversive emotion would each be salient dimensions of visual stimuli, and evoke significant modifications in behaviour (measured by reaction time and delayed recognition memory) and in neurofunction (measured by the BOLD response) in a predefined subcortical network consisting of the midbrain, hippocampal formation, amygdala and ventral striatum/pallidum.

2. There would be significant behavioural and neurofunctional interactions between the effects of each salience dimension.

2.4 Experimental Procedure

2.4.1 Phase 1 - Practice task

Before the task was performed, participants were given identical verbal and visual aided instructions for the task and told the reward contingencies. They were then given a practice run of the task outside the scanner where comprehension of the instructions and performance was ensured. The practice task was terminated when 10 continuous perfect trials were completed; all participants achieved this level of performance within 3 minutes. Directly following the practice task participants were given the money earned in cash (up to £1). This practice session minimized learning effects during functional data acquisition and was intended to lead to a switching of reward responses from the moment of reward receipt to the time of reward predicting cue**.** Participants were then shown the money they could win in cash (£40) prior to entering the scanner.

2.4.2 Phase 2 - Prefamiliarisation task

Following the practice task, participants were familiarised with half of the 280 different picture cue stimuli to be used in the online task, chosen pseudorandomly to be balanced

across Emotional and Reward categories. The IAPS emotional rating of each picture was balanced across other categories (figure 2.2). Each picture was presented 3 times for 1000ms on a grey background in a randomised order. To reinforce reward contingencies and ensure category validity participants were instructed to attend to whether each picture was indoor or outdoor.

2.4.3 Phase 3 - Online task

Following the familiarisation task participants performed the full SIT task whilst functional MRI data was acquired. Online button presses and reaction times were recorded along with heart rate and estimated oxygen saturation using a finger probe pulse oximetry monitor.

2.4.4 Phase 4 - Recognition task 1hr delay

One hour following the conclusion of the online task participants were shown 140 of the picture cues (balanced across all 8 categories) randomly mixed with 68 new distractor pictures (17 indoor-neutral, 17outdoor-neutral, 17 indoor-emotional, 17 outdoor-emotional). The average IAPS emotional rating of the new emotional distractor pictures was matched to the ratings of the studied pictures (figure 2.2). Participants received identical verbal and visual instructions for the recognition task, which consisted of 3 judgments cued by text underneath each picture. Participants were asked to indicate with a button press first if they recognised the pictures ('Old' or 'New') and if they did then rate their confidence in their memory (Duzel et al., 1997). For pictures judged as 'New' they were asked to specify their confidence in that judgment ('Sure' or 'Guess'). Finally they were asked to rate how distressing they found the picture when first viewed by moving a slider along a Visual Analogue Scale from 'Not Distressing' to 'Very Distressing' (figure 2.4). This was to ensure validity of individual experiences of emotional arousal for each emotional category picture.

The time limits for the 3 steps in the recognition task were 3000ms, 4000ms and 5000ms respectively.

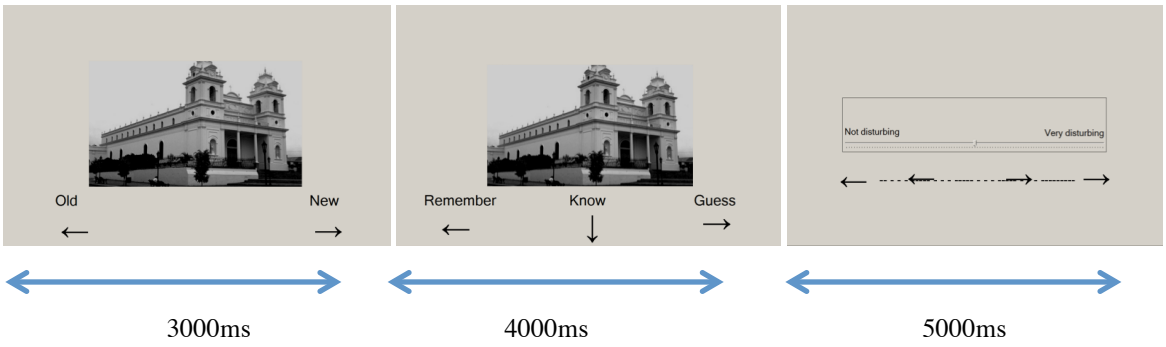


Figure 2.4 - Recognition procedure performed at 1hr and 24hr. Participants judged whether scenes were new or old, then rated their confidence in that judgement and how emotionally distressing they found the pictures when first seen.

2.4.5 Phase 5 - Recognition task 24hr delay

24 hours after the conclusion of the online task participants were asked to perform the recognition task with the remaining 140 pictures, again randomly mixed with 68 category-balanced and emotional arousal- matched distractors.

2.5 Methods

2.5.1 Participants

Twenty-nine healthy adults were recruited, mostly by word of mouth from other healthy and disease participants, and where this was not possible, by local advertisement. The target age, gender, education and geography were determined by the demographic features of the ARMS participants (chapter 3). Participants were excluded if they had a personal or family history of neurological or psychiatric disorder or met criteria for a current or past substance use disorder (DSM IV Harmful use of substances or Substance dependence disorders). Participants gave

written consent to participate in the study which was approved by the Hammersmith Hospital Research Ethics Committee.

On the morning of the MRI scan, participants provided a urine sample for drug screening (Triage UDS kit, Alere Ltd. UK) and pregnancy testing (Clearview HCG, Alere Ltd. UK), and performed an alcohol breath test (Lion Alcometer SD400, Lion Laboratories Ltd, UK). Height, weight, lying blood pressure and resting heart rate were recorded, and participants completed an MRI safety questionnaire conducted by the research radiographer. Left/right hand dominance was determined using the Handedness Inventory (L. J. Chapman & Chapman, 1987). Participant demographics are provided in table 2.1

Demographics

Age : Mean(SD) years	23.9 (4.4)
Gender (M:F)	14:15
Years Education: Mean (SD)	11.9 (2.4)
Handedness (R:L handed)	25:4
Black/mixed: white	9:20

Table 2.1 Demographic data for healthy participants

2.5.2 Clinical data

Prior to scanning, I assessed all participants using a clinical psychiatric interview covering current and past psychiatric and medical history, development, occupational and social history, medication, family history, and current mental state examination. Clinician scales were administered as follows: Hamilton Anxiety and Depression rating scales, Comprehensive Assessment of At Risk Mental States

2.5.3 Behavioural analyses

Two measures of behavioural salience were recorded - reaction time (RT) and recognition accuracy.

In order to compare reaction time, averages for each of 8 trial types (2[Reward] x2[Novelty] x2[Emotion]) were calculated for each participant. These were then entered into a repeated measures ANOVA in SPSS v19 (IBM) with Reward, Novelty and Emotion as within participant factors. The main effect of each factor was examined, as well as the 2-way interactions between factors. To aid interpretation I did not examine 3 way interactions.

Analyses of recognition rates were conducted for the 1hr and 24hr sessions separately, and utilized measures of both hit rate and discrimination accuracy, correcting for false alarms ('new' pictures recognised falsely as old) according to the following formulae from Signal Detection Theory (Corwin, 1994):

Hit Rate (HR) = (Hits +0.5)/(Total Old +1)

False Alarm Rate (FAR) = (False Alarms + 0.5)/(Total New + 1)

Discrimination Accuracy (DA) = HR - FAR

These were then entered into repeated measures ANOVAs in SPSS with Reward, Novelty and Emotion as within participant factors.

2.5.4 fMRI analyses

MR images were acquired on a 3T Siemens Tim Trio (Siemens Healthcare, Erlangen, Germany) using the 32-channel phased array head coil. Anatomical reference images were acquired using a dual-contrast B1-homogeneity correcting modification of the Magnetization Prepared Rapid Acquisition of Gradient Echo (MPRAGE) sequence [1] known as MP2RAGE [2]. 1mm isotropic resolution was acquired using TR=5s, TE=2.96ms, 256x240x176mm FOV, a 4 degree flip angle, inversion times of 700 and 2500ms, and a parallel imaging factor of 3 in 8m:22s.

T2*-weighted echo-planar (EPI) images were acquired for both functional tasks and the resting-state scan, using 3.5x3.5x3mm resolution in a 225mm in-plane FOV, TR=2s, two echo times of 13 and 31 ms, 80 degree flip angle, 36 slices in each TR, and a parallel imaging factor of 2. These volumes covered the hippocampus, amygdala, brainstem (including diencephalon, mesencephalon, pons, and medulla oblongata), and neocortex excluding the vertex. 788 volumes were acquired per session.

The fMRI data were preprocessed and statistically analyzed using a general linear model (GLM) approach (Friston, Holmes, & Worsley, 1994) as implemented in SPM8 (Wellcome Department of Cognitive Neuroscience, University College, London, UK) within MATLAB 7.1 (The Mathwork Inc.). Prior to preprocessing all scans with scan-to-scan movement greater than 1mm translation or 1.5^0 rotation were automatically detected and checked for artefact. Following this all acquired scans were further manually checked for significant susceptibility by motion stripe or other type artefacts. Artefactual scans were removed and replaced by time-averaging adjacent scans, and a 'dummy' regressor of no interest was created for each participant which corresponded to the removed artefactual scans ensuring these scans were excluded from analysis.

All functional images were then further corrected for motion artefacts by realignment to the first volume using the realignment procedure in SPM8. Spatial normalization was performed by first coregistering the T1 scan to the first volume of the realigned EPI sequence and segmenting the T1 scan into grey matter, white matter and CSF compartments. These 3 compartments were then warped to their respective Tissue Probability Maps (TPMs) in SPM8. The EPI normalization was realized by then applying the T1 warping parameters to the functional images. The images were resampled to 2 x 2 x 2 mm and smoothed with an isotropic 8 mm full-width half-maximum Gaussian kernel. The time-series fMRI data were highpass-filtered (cutoff 128 s) and globally scaled over voxels and scans within each session.

A statistical model for each participant was computed by applying a canonical Hemodynamic Response Function (HRF Friston et al., 1998) to each of the 8 regressors of interest generated by the SIT corresponding to the timepoint of picture cue presentation (2[Reward] x 2 [Novelty] x 2[Emotion]). To capture residual task related brain activity we also included regressors corresponding to No-Go cues and at reward and non-reward outcomes. To capture movement-related artefacts, six covariates per session were included (the three rigid-body translations and three rotations determined from initial realignment) as was an individual participant error covariate corresponding to trials where participants failed to press the button to 'Go' trials (Omission Errors), or pressed the button to 'NoGo' trials (Commission Errors).

Regionally specific condition effects were tested by employing linear contrasts for each participant. The resulting contrast images were submitted to a second level random-effects analysis. Here, one-sample t tests were used on images obtained for each participants' volume set and different conditions. In order to more accurately visualize activation patterns a study specific brain image template was created by applying warping parameters obtained during the segmentation procedure to the individual T1 scans and time-averaging across all included participants (figure 2.5).

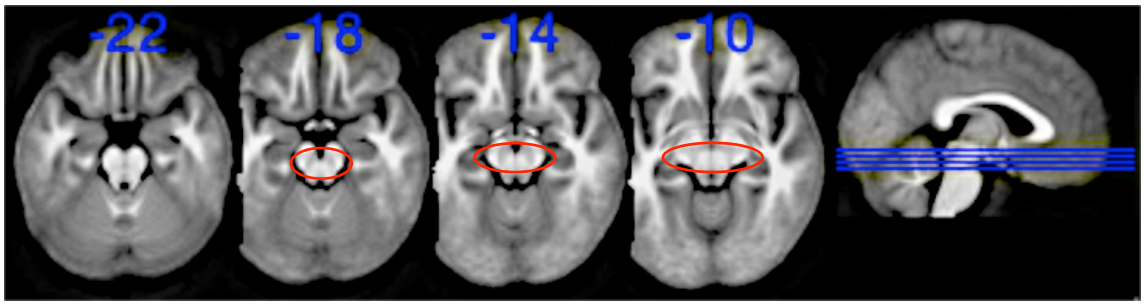
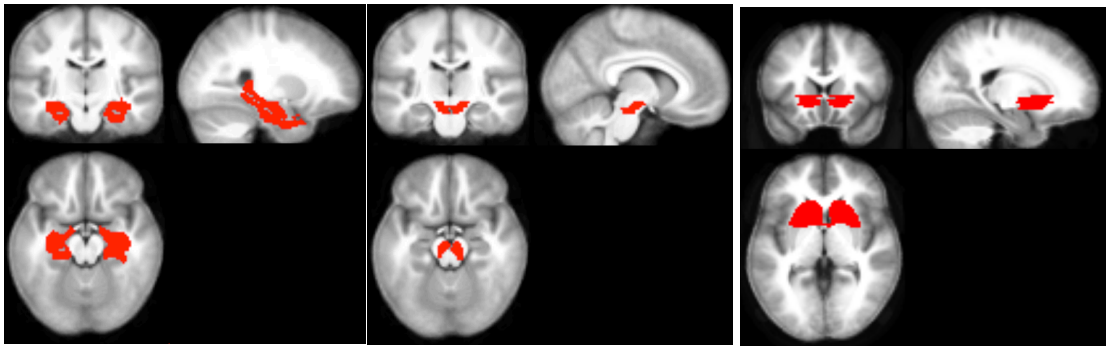


Figure 2.5: Illustrative midbrain slices on MP2RAGE T1 sequence with visible Substantia Nigra/VTA regions circled in red

I defined four primary regions of interest derived from the Grace model relevant to my hypotheses (section 1.5.1): the midbrain, hippocampus/parahippocampal gyrus, amygdala and ventral striatum/pallidum. For the amygdala and hippocampus/parahippocampal regions of

interest we used anatomical masks from the automated anatomical labeling toolbox implemented in SPM 8 (Tzourio-Mazoyer et al., 2002). For the midbrain region of interest I visualized the substantia nigra/VTA as bilateral dark stripes in midbrain slices on the acquired mp2rage T1 sequence (figure 2.5, z=-20 to z= -10) and created a study specific mask using Mricron software (figure 2.6B http://www.mccauslandcenter.sc.edu/ mricro/mricron/) based on the landmarks in Bunzeck et al (2006). The ventral striatum/pallidum region of interest (figure 2.6C) comprised the ventral anterior portion of the head and body of caudate, nucleus accumbens, ventral putamen and pallidum. Other regions known to be involved in processing rewarding/novel/emotional stimuli include the orbitofrontal and inferior frontal cortex (Schultz, O'Neill, Tobler, & Kobayashi, 2011) anterior cingulate cortex and insula (Fiddick, 2011) and precuneus (Dörfel, Werner, Schaefer, Kummer, & Karl, 2009) were not included in the ROI analysis but explored in a whole brain analysis. Given the limited anatomical a priori hypotheses I thresholded the analysis at $p<0.005$, with a minimum cluster size of 3 voxels. Following the relevant ROI small volume correction results were thresholded at $p<0.05$ Family Wise Error (FWE) corrected.



A B C

Figure 2.6 Average T1 for healthy control participants with masks superimposed A. Hippocampus/PHG mask B. SN/VTA mask C. Ventral striatum/pallidum mask

2.6 Results

2.6.1 Behavioural Results

2.6.1.1 Task Performance

All participants complied well with the practice SIT, online SIT, and delayed recognition tasks demonstrating good comprehension of task instructions and the sustained attention required to perform the tasks. Table 2.2 presents rates of Omission Errors (failure to press the button during Go trials) and Commission trials (pressing the button during NoGo trials), and rates of no response trials during Recognition tasks. In subsequent behavioural and fMRI analyses, error trials (both omission and commission errors) were excluded.

Task Performance in healthy participants

Task	% Errors- Mean (SD)
SIT - Go Trials (Omissions)	4.03 (5.94)
SIT - No Go Trials (Commissions)	10.25 (10.26)
Recognition 1hr (no response)	7.14 (9.75)
Recognition 24hr (no response)	5.51 (6.98)

Table 2.2 SIT and Recognition task performance in healthy control participants

2.6.1.2 Reaction time

I examined the effects of the task on time to button press, although outcome was not contingent upon reaction time. Reaction time reflects several relevant cognitive processes including attention, orientation, response selection and motor action; I considered both speeding and slowing of reaction time away from the mean as possible surrogate markers of the behavioural salience of a stimulus.

There was no main effect of reward on reaction time ($F(28,1)=0.198$, $p>0.1$). There was an effect of novelty on reaction time ($F(28,1)=4.443$, $p=0.044$), with participants responding faster to familiar than to novel trials (novel trials mean(SD)=608.5(17.5)ms, familiar trials 603(17.6)ms). There was also an effect of emotion ($F(28,1)=6.338$, $p=0.017$), with participants responding slower to emotional than to neutral trials (emotional trials mean(SD)=612.8(19.1)ms, neutral trials mean(SD) = 598.7 (16.3) ms, figure 2.7).

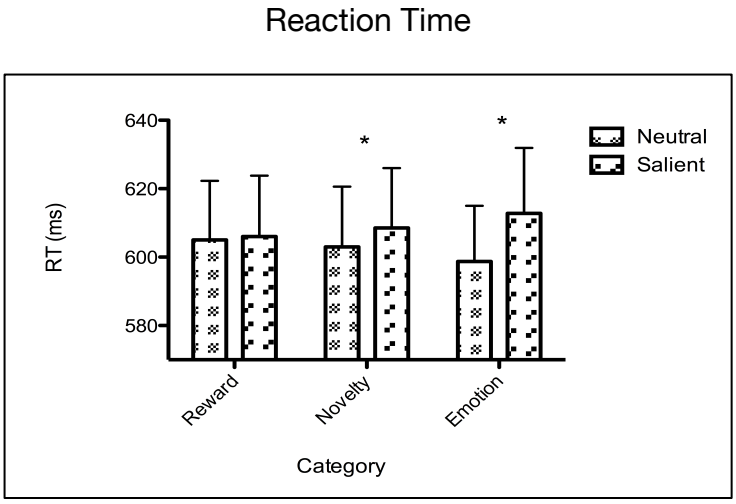


Figure 2.7 Mean (SD) Reaction time for main effects of Reward Novelty and Emotion. 'Salient' category refers to Reward predicting, Novel or Emotional stimuli, * $p<0.05$.

The effect of emotion in slowing reaction times was enhanced in the presence of both reward and familiarity; there were significant interactions on RT between Reward and Emotion ($F(28,1)=15.536$ $p<0.0001$, figure 2.8a), and between Novelty and Emotion ($F(28,1)=-5.67$, $p=0.024$, figure 2.8b). In non-reward trials emotion had little effect, but in reward trials emotion had a large effect in further slowing reaction time. Reactions were generally faster to familiar trials, but not in emotional trials. There was no significant interaction between Reward and Novelty ($F(28,1)=0.037$, $p>0.1$, figure 2.8c).

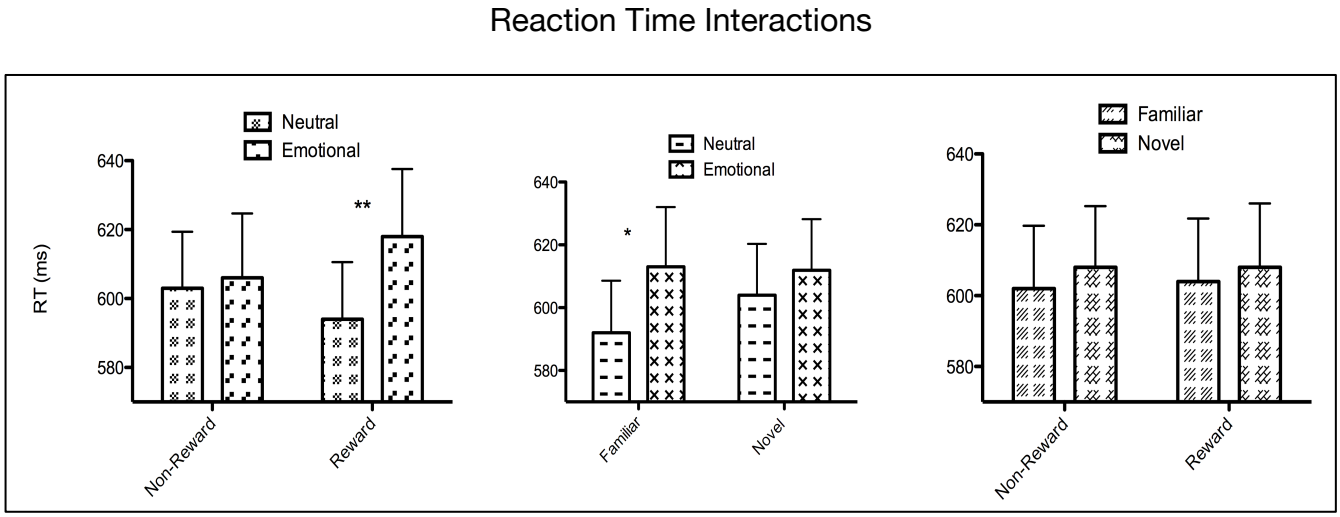


Figure 2.8 Mean (SD) Reaction times for 2way interactions. A Reward x Emotion, B Novelty x Emotion, C Reward x Novelty . *p<0.05 **p<0.01

Given these interactions, I re-examined the main effects of reward and novelty in neutral cues alone, excluding emotional trials. There was a trend for faster responding to reward-predicting than non-reward-predicting cues ($F(28,1)=4.01$, $p=0.055$, reward-predicting cues mean(SD)=594.2(16.6)ms, non-reward predicting cues 603.2(16.4)ms), and a significant effect of novelty ($F(28,1)=9.81$, $p=0.004$, novel trials mean(SD)=605(16.3)ms, familiar trials 592.4(16.6)ms - figure 2.9).

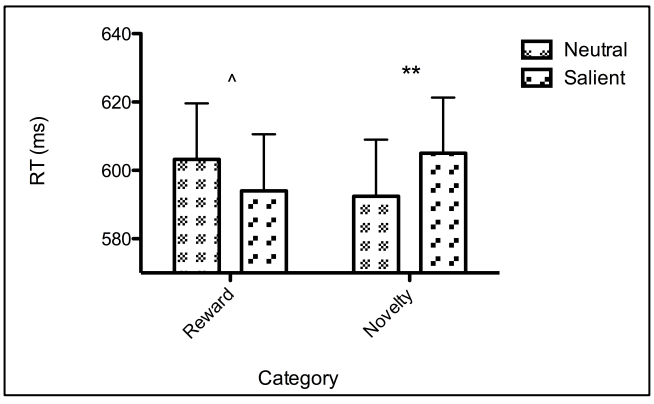


Figure 2.9 Mean (SD) Reaction time for main effects of reward and novelty in neutral (non-emotional) trials *p<0.05 **p<0.01 ^p<0.1. Salient category refers to Reward predicting or Novel stimuli.

2.6.1.3 Recognition

I analysed each of the main effects of reward novelty and emotion and their 2-way interactions at 1hr, more reflecting memory encoding processes, and at 24hr, more reflecting consolidation processes (Lisman et al., 2011).

Main Effects

At 1hr the overall average recognition correct hit rate (HR: % old cues correctly recognised as old) was 66.7% (dotted line, figure 2.10A). There were significant effects of each of the cue factors reward, novelty and emotion (figure 2.10A). Reward-predicting cues were significantly better recognised than non-reward predicting cues (+9.8%, $F(28,1)=34.7$, $p<0.001$), novel cues were less recognised than familiar cues (-15.4%, $F(28,1)=83.7$, $p<0.0001$;), and emotional cues better recognised than neutral cues (+19.4%, $F(28,1)=45.3$ $p<0.0001$).

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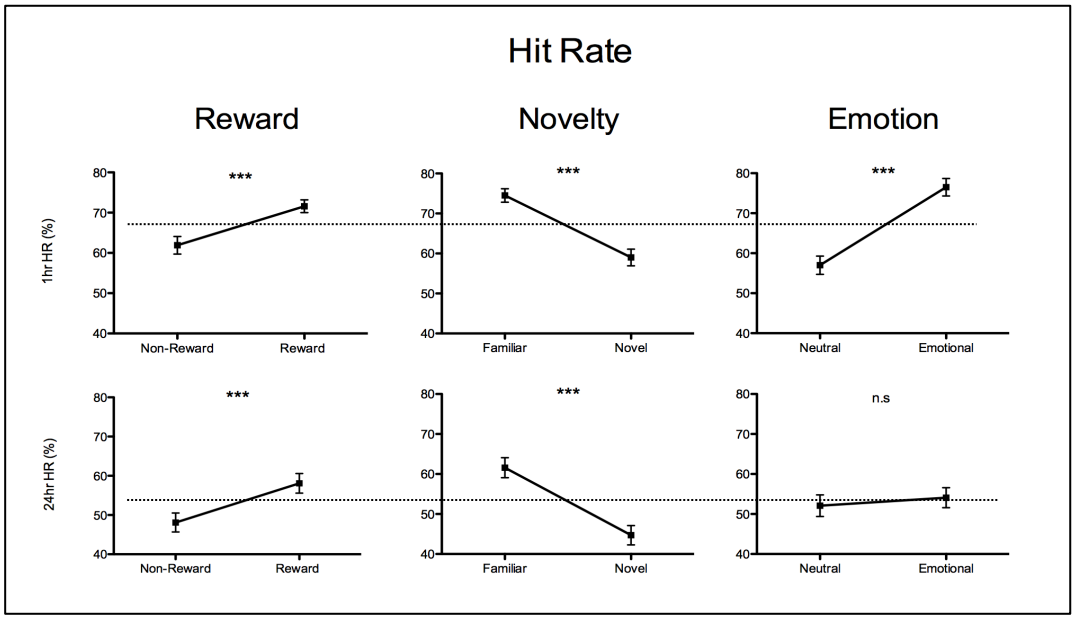

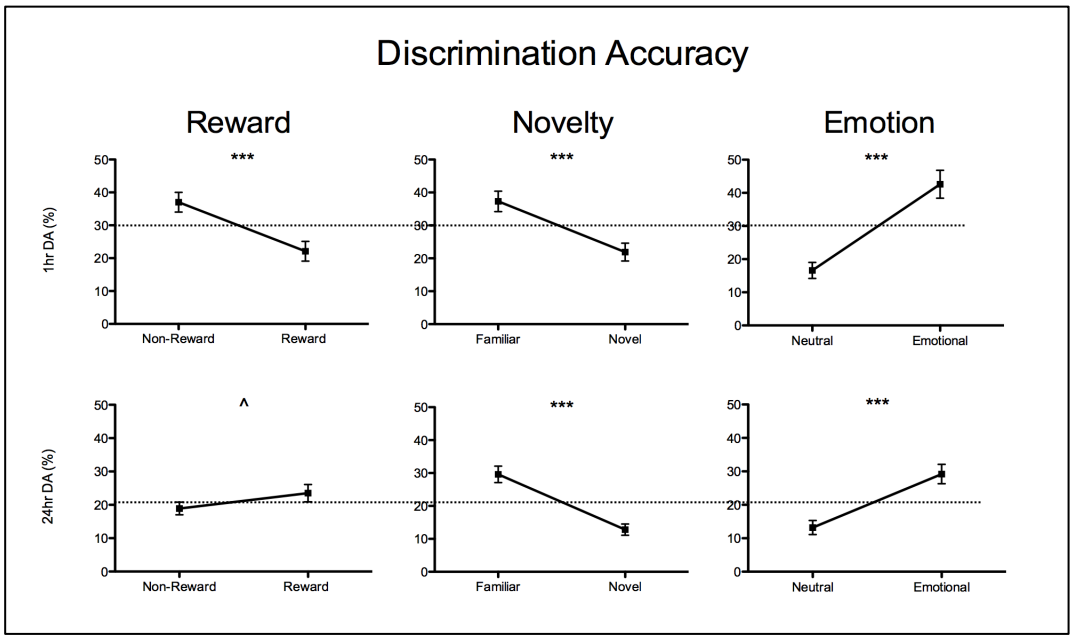

Figure 2.10
Mean (SD) A) recognition hit rate (HR) B) discrimination accuracy (DA) and C) False Alarms (FA) for at 1hr and at 24hr. Dotted lines represent overall session mean rate, the slope of the line away from the mean reflects the influence of that factor on the specified outcome. Hit rate refers to % old cues correctly recognised as old, false alarms refers to % new cues falsely recognised as old, discrimination accuracy refers to hit rate adjusted for false alarm rate. * $p<0.05$ ** $p<0.01$ *** $p<0.001$

At 24hr the overall mean hit rate was 53.1%. Effects were similar for reward (+10.0% F(28,1) =26.6 p<0.0001) and novelty (-16.9% f(28,1)=73.4 p<0.0001), but there was no longer a significant benefit of emotion (+2.0% F(28,1)=0.524 p=0.475).

However when hit rates were corrected for false alarms (new cues recognised as old, figure 2.11) to give discrimination accuracy (DA) rates (figure 2.10b) there was a reversal of the effects of reward at 1hr (overall 1hr mean DA = 29.6%, reward related difference -14.9%, F(28,1)=29.8 p<0.0001, Figure 2.10b). This reflected a large significant increase in false alarm (FA) rate at 1hr to Reward predicting cues (overall 1hr mean FA = 37.2%, reward related difference +24.7%, F(28,1)=87.6, p<0.0001, figure 2.10c). By 24hr this effect was reduced, and this revealed a trend towards increased discrimination accuracy for rewarding cues relative to non rewarding cues (overall 24hr mean DA = 21.2%, reward related difference +4.6 % F(28,1)=3.55 p=0.07, figure 2.10b). In contrast there was a decrease in false alarms at 1hr to emotional cues (mean difference -6.5%, F(28,1)=8.2, p=0.008, figure 2.10c), leading to improved discrimination accuracy for emotional cues (mean difference +26%, F(28,1)=66.9 p<0.0001). By 24hr this effect was increased, so that although there was no effect of emotion on hit rate during this session, there was increased discrimination accuracy for emotional cues at 24hr (mean difference +15.9%, F(28,1)=28.2, p<0.0001) .

Interactions

As with reaction time, there were significant interactions between emotion and both reward and novelty on recognition during both sessions, but no interactions between reward and novelty (figure 2.12). At 1hr the hit rate recognition boosting effects of reward were reduced in emotional trials compared to neutral trials (F(28,1)=6.85 p=0.014); in contrast the recognition boosting effects of familiarity were enhanced in emotional trials, at trend level significance (F(28,1)=3.49 p=0.072). At 24hr both of these interactions were further accentuated (figure 2.12).

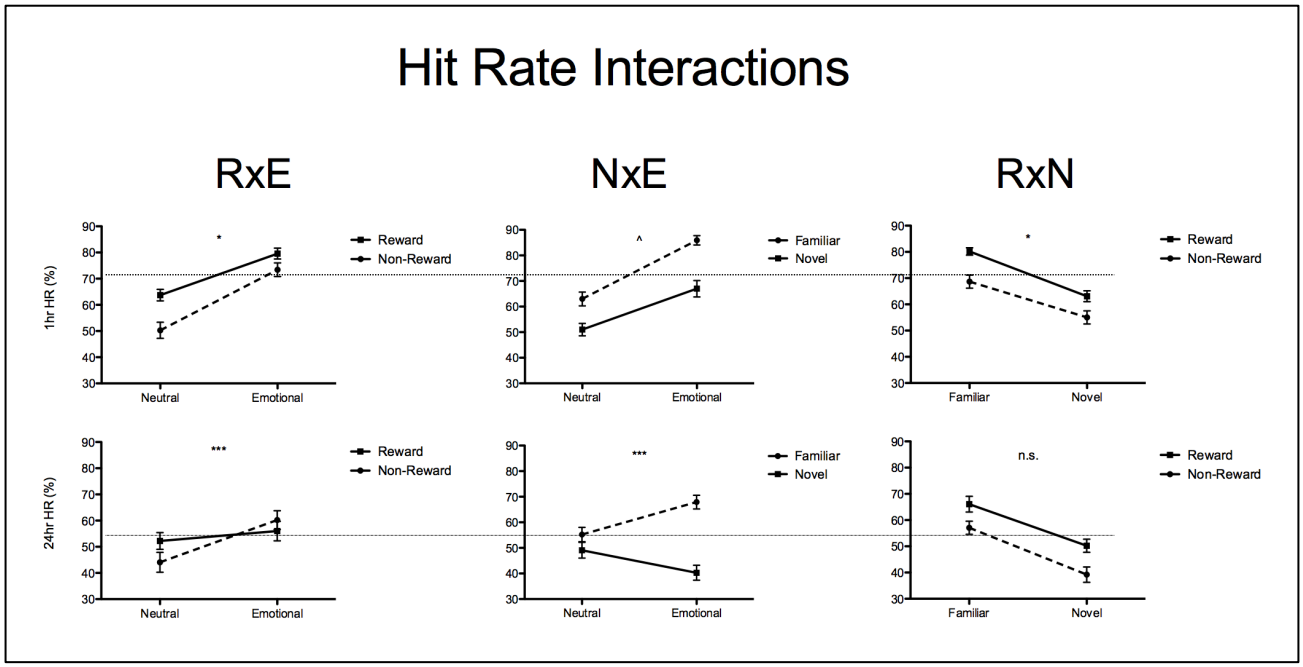

Figure 2.11 - Mean (SD) recognition hit rate and discrimination accuracy interactions. R: Reward, N: Novelty, E: Emotion. n.s. not significant, * p<0.05 **p<0.01 . Dotted lines represent means.

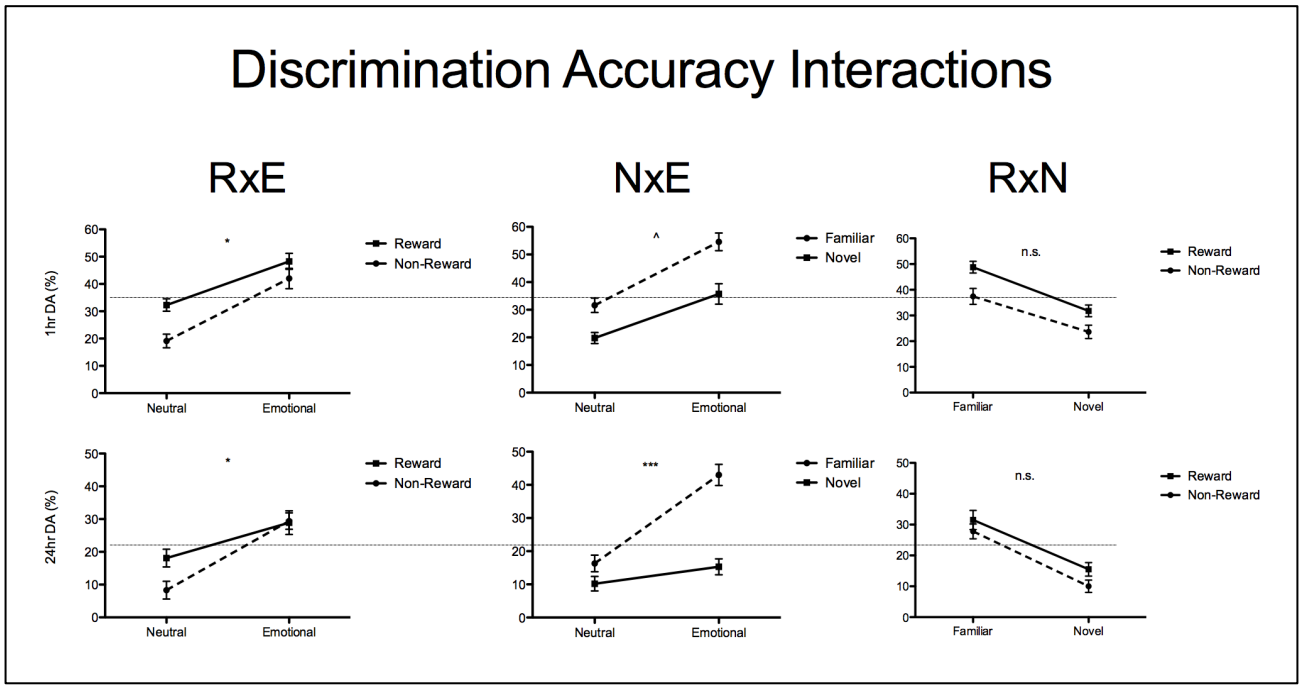

Figure 2.12 - Mean (SD) recognition hit rate and discrimination accuracy interactions. R: Reward, N: Novelty, E: Emotion. n.s. not significant, * p<0.05 **p<0.01 . Dotted lines represent means

For discrimination accuracy, interactions were similar, and also accentuated at 24hr relative to 1hr (figure 2.12). There were no interactions between Reward and Emotion on False Alarm Rate (figure 2.13), and false alarms cannot be examined for the effects of novelty.

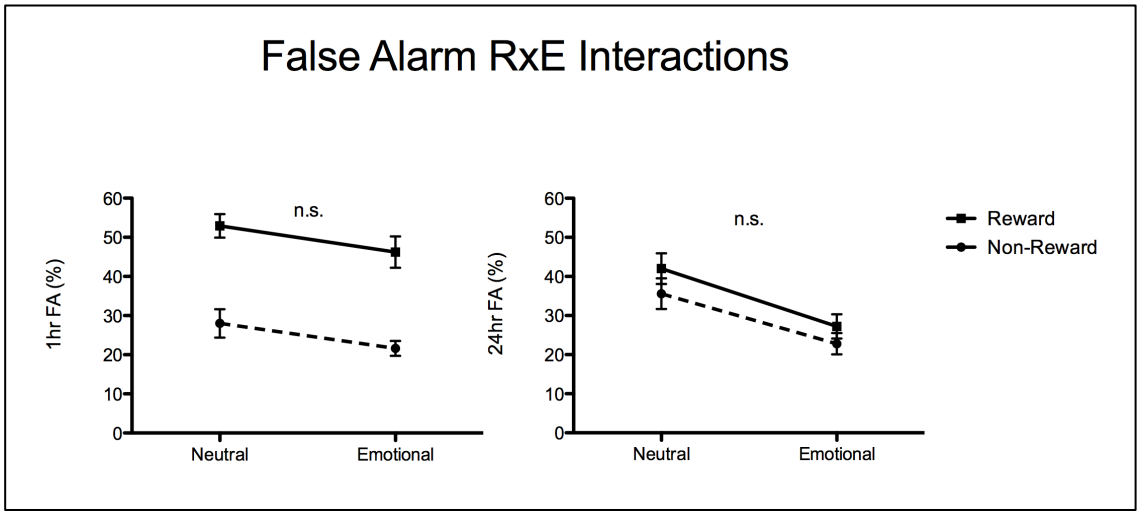

Figure 2.11 - Mean (SD) recognition hit rate and discrimination accuracy interactions.
R: Reward, N: Novelty, E: Emotion. n.s. not significant, * $p<0.05$ ** $p<0.01$

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2.6.2 fMRI

2.6.2.1 Reward

Within the primary ROI network (midbrain, hippocampus, amygdala, ventral striatum) there was significant activation to reward prediction (all reward predicting cues greater than non-reward predicting cues) in the midbrain (table 2.3, figure 2.12).

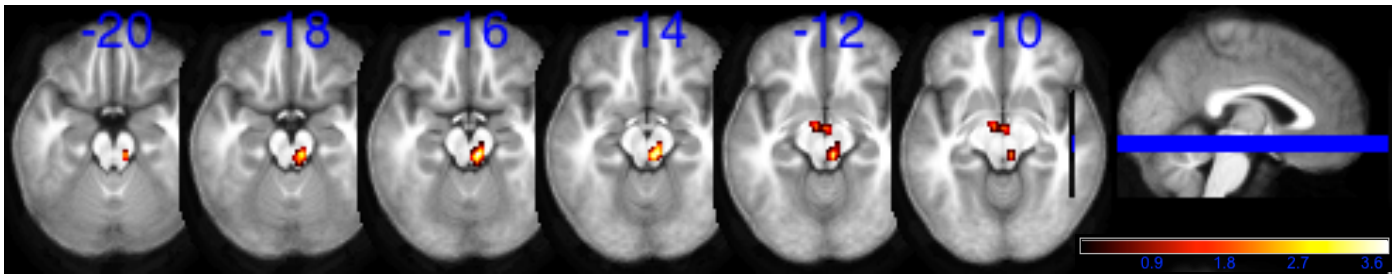

Figure 2.12. fMRI activations to Reward within the primary ROI network. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p<0.005

Outside these ROIs there was also activation in the middle frontal gyri bilaterally, and in large bilateral clusters in the secondary visual areas including lateral occipital cortices extending to bilateral lingual and fusiform gyri (table 2.3 figure 2.13).

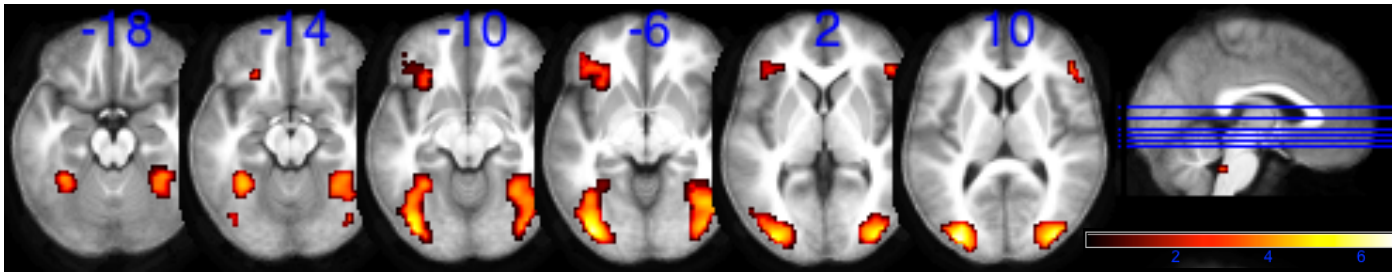

Figure 2.13. fMRI activations to Reward outside the primary ROI network. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p<0.005

For the reverse contrast (i.e. non-reward predicting cues greater than reward predicting cues) there was no activation in the primary ROI network, but there was activation in the medial

occipital areas around the calcarine sulcus, and in insulae and superior temporal gyri bilaterally (table 2.3, figure 2.13).

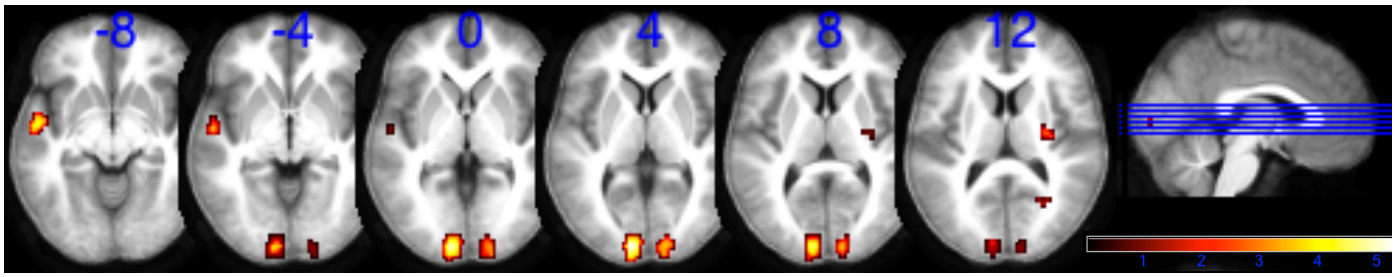

Figure 2.13. fMRI activations to Reward predicting cues<Non-reward predicting cues within the whole brain. Z coordinates are displayed in blue. Images are displayed for visualisation at whole brain uncorrected p<0.005

2.6.2.2 Novelty

For the main contrast of cue novelty (all novel cues greater than familiar cues) there was significant activation within primary ROIs in bilateral hippocampal clusters including posterior and mid-hippocampal and parahippocampal regions, and in the anterior hippocampus (entorhinal cortex) -amygdala complex bilaterally (table 2.3 figure 2.14).

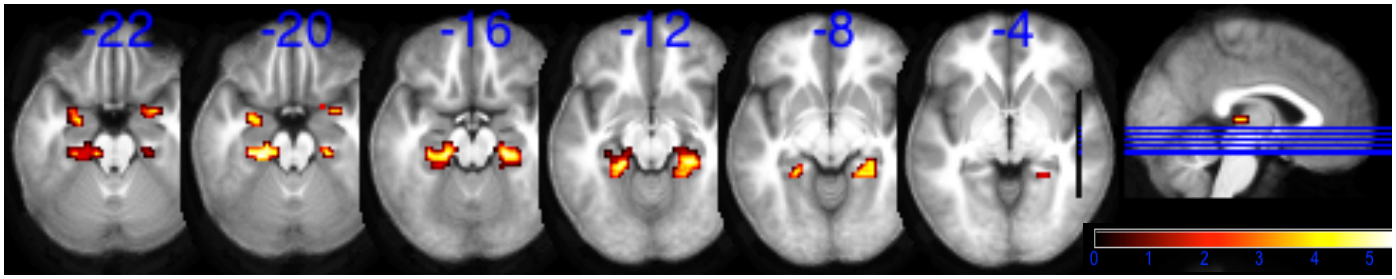

Figure 2.14. fMRI activations to Novelty within the primary ROI network. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p<0.005

Table 2.3 List of fMRI BOLD associated activations to main effects and interactions in healthy controls within the primary ROI network

		size	peak						
Contrast	+/-	k	p(FWE WB)	p(FWE ROI)	T	Z	p(unc)	x,y,z (MNI)	Location
Reward	Pos	19	0.739	0.014	3.95	3.49	<0.001	6 -28 -17	R midbrain
		3	0.998	0.119	3.12	2.86	0.002	-6 -7 -11	L midbrain
		3	1	0.149	2.89	2.68	0.004	0 -10 -11	L midbrain
	Neg	NIL							
Novelty	Pos	73	0.315	0.02	4.51	3.88	<0.001	24 -43 -11	R PHG
			0.045	0.043	4.13	3.62	<0.001	27 -37 -11	R Hipp (Subic)
			0.675	0.063	3.98	3.51	<0.001	24 -28 -17	R Hipp (Subic)
		69	0.411	0.035	4.35	3.77	<0.001	-21 -37 -14	L PHG
			0.528	0.041	4.18	3.65	<0.001	-27 -31 -17	L Hipp (Subic)
			0.563	0.045	4.13	3.62	<0.001	-18 -28 -17	L Hipp (Subic)
		13	0.991	0.058	3.2	2.93	0.002	-27 -4 -20	L Amyg -Hipp (EC)
		13	0.994	0.068	3.15	2.89	0.002	24 5 -26	R Amyg-Hipp (EC)
	Neg	NIL							
Emotion	Pos	166	0.002	<0.001	6.93	5.24	<0.001	21 -4 -17	R Amyg (SF)
			0.006	<0.001	6.5	5.03	<0.001	27 -7 -35	R Hipp (EC)
		16	0.006	<0.001	6.49	5.03	<0.001	18 -34 1	R Hipp (CA)
		237	0.023	<0.001	5.86	4.69	<0.001	-18 -34 -2	L Hipp (Subic)
			0.028	<0.001	5.76	4.64	<0.001	-24 -4 -20	L Amyg (LB)
			0.107	<0.001	5.14	4.28	<0.001	-27 -4 -32	L Amyg (LB)
	Neg	21	0.019	<0.001	5.93	4.74	<0.001	27 -43 -8	R Ling g/Hipp (Subic)
		10	0.049	0.005	5.51	4.49	<0.001	-30 -43 -5	L Hipp (CA)
		14	0.276	0.01	4.65	3.97	<0.001	12 17 -11	R N Acc
RxE		15	0.998	0.07	3.16	2.9	0.002	24 -04 -17	R Amygdala (LB)
		9	0.531	0.039	4.28	3.72	<0.001	27 -43 -8	R PHG
		5	0.999	0.349	3.13	2.87	0.002	-24 -43 -5	L PHG
NxE		14	0.977	0.164	3.17	2.91	0.002	12 17 -11	R Caudate
		18	0.987	0.191	3.08	2.84	0.002	-18 17 -5	L Putamen
RxN		3	0.998	0.07	3.19	2.92	0.002	9 -25 -20	R Midbrain
		39	0.702	0.018	4.01	3.54	<0.001	21 5 -20	R Hipp (EC)/Amyg
		8	0.992	0.27	3.27	2.98	0.001	-18 -28 -14	L Hipp (Subic)

Abbreviations: Subic: subiculum, Amyg: Amygdala, Hipp: Hippocampus, EC: Entorhinal cortex, LB: Laterobasal, SF: superficial group, CA: Cornu Ammonis, Ling g: Lingual gyrus, FWE: Family Wise Error, WB: Whole Brain, PHG: Parahippocampal gyrus ROI: Region of interest, unc: uncorrected

Table 2.4 List of fMRI BOLD associated activations to main effects and interactions in healthy controls outside the primary ROI network.

		cluster size	peak					
Contrast	+/-	k	p(FWE WB)	T	Z	p(unc)	x,y,z (MNI)	Location
Reward	Pos	563	0.002	6.95	5.25	<0.001	-39 -85 -8	R Occip (V4)/Fusiform g
		583	0.021	5.88	4.71	<0.001	36 -85 10	R MOg/IOg/ITG
		35	0.69	4.02	3.54	<0.001	51 29 7	R IFG P. Triangularis
		73	0.939	3.56	3.21	0.001	24 -58 43	R IPL/SPL
		100	0.943	3.55	3.2	0.001	-39 32 -5	L IFG P. Orbitalis/Insula
		41	0.986	3.33	3.03	0.001	-24 -70 34	L SOg /SPL
	Neg	91	0.07	5.33	4.39	<0.001	-9 -94 4	L SOg
		40	0.547	4.21	3.67	<0.001	-54 -7 -8	L STG
		10	0.946	3.54	3.19	0.001	57 -7 -11	R STG
		48	0.961	3.48	3.15	0.001	12 -94 7	R Calcarine g
Novelty	Pos	267	0.057	5.37	4.41	<0.001	24 -46 -14	R Occip (V4)/Fusiform g/ITg
		332	0.216	4.72	4.01	<0.001	-24 -40 -14	L Occip (V4)/Fusiform g
		121	0.355	4.44	3.83	<0.001	39 -85 10	R MOg
		14	0.933	3.52	3.17	0.001	24 11 -23	R Parahippocampal g
		35	0.933	3.52	3.17	0.001	42 14 -17	R Temporal Pole
		31	0.951	3.46	3.13	0.001	57 -16 34	R PCG
	Neg	94	0.755	3.86	3.43	<0.001	9 -64 37	R Precuneus
		22	0.941	3.49	3.15	0.001	-9 -67 28	L Precuneus
Emotion	Pos	2152	<0.001	11.29	6.88	<0.001	45 -76 -5	R Occip (V4)/Fusiform g
			<0.001	8.83	6.06	<0.001	42 -64 16	R MTG
		2326	<0.001	10.65	6.68	<0.001	-36 -43 -23	L Occip (V4)/Fusiform g
		45	<0.001	9.27	6.22	<0.001	33 -7 -38	R Fusiform g
		1184	0.002	6.9	5.23	<0.001	-39 29 -14	L IFG P. Oritalis
		890	0.004	6.71	5.14	<0.001	39 11 25	R IFG P. Opercularis
		428	0.011	6.2	4.88	<0.001	-6 50 28	L SMg
		62	0.011	6.17	4.86	<0.001	18 -31 1	R Thalamus - temporal
		129	0.118	5.09	4.25	<0.001	-24 -55 49	L SPL
		60	0.418	4.41	3.81	<0.001	51 -7 -17	R MTG
		34	0.461	4.34	3.77	<0.001	-3 41 -17	L Rectal/Mid Orbital g
		14	0.512	4.27	3.72	<0.001	24 5 -23	R Parahippocampal g
		32	0.852	3.78	3.37	<0.001	-51 -7 -17	L MTG
	Neg	475	0.008	6.35	4.96	<0.001	-27 -46 -5	L Lingual g
		76	0.017	6	4.77	<0.001	27 -46 -8	R Lingual/Fusiform g
		128	0.075	5.31	4.38	<0.001	36 29 40	R MFg/SFg
		73	0.222	4.77	4.05	<0.001	60 -16 4	R STG
		461	0.244	4.72	4.01	<0.001	27 50 4	R MTG/Mid Oribtal g
		148	0.613	4.13	3.62	<0.001	48 -55 49	R IPL/SMg
		47	0.701	4.02	3.54	<0.001	-57 -10 4	L STG
		58	0.844	3.79	3.38	<0.001	-15 -7 25	L dorsal Caudate

		cluster size	peak					
Contrast	+/-	k	p(FWE WB)	T	Z	p(unc)	x,y,z (MNI)	Location
RxE		290	0.131	5.07	4.23	<0.001	-30 -88 -8	L IOg/Fusiform g/V4
		240	0.357	4.54	3.89	<0.001	27 -94 -2	R IOg/Fusiform g/V4
		27	0.548	4.25	3.7	<0.001	-36 -1 37	L PCC
		15	0.992	3.3	3.01	0.001	-51 -64 7	L MTG
		56	0.331	4.58	3.92	<0.001	-24 -46 -5	L lingual /Calcarine g
		21	0.562	4.23	3.69	<0.001	30 -46 -8	R Lingual g
NxE		571	0.043	5.37	4.41	<0.001	-9 -97 10	L/R SOg/occip pole
		170	0.168	4.71	4.01	<0.001	-27 50 10	L MFG
		107	0.592	3.95	3.49	<0.001	45 -49 52	R IPL
		98	0.66	3.85	3.42	<0.001	0 -22 25	L MCC/PCC
		38	0.772	3.69	3.3	<0.001	-42 -64 -20	L Fusiform g/V4
		129	0.78	3.68	3.29	<0.001	33 47 4	R MFG
		213	0.83	3.59	3.23	0.001	9 -70 37	R/L Precuneus
		182	0.877	3.5	3.16	0.001	24 32 40	R MFG
RxN		27	0.119	5.09	4.25	<0.001	24 8 -20	R temporal pole
		374	0.28	4.65	3.97	<0.001	39 -79 -2	R IOG (V4)/R ITG
		58	0.418	4.41	3.81	<0.001	-33 26 -14	L IFG (p. Orbitalis)/POr g
		262	0.505	4.28	3.72	<0.001	-36 -46 -20	L Fusiform g/MOg
		53	0.515	4.27	3.71	<0.001	-57 -10 7	L STG
		31	0.833	3.81	3.39	<0.001	-57 -31 7	L MTG
		33	0.92	3.63	3.26	0.001	18 -58 -26	R Cerebellum
		82	0.933	3.6	3.23	0.001	42 -7 28	R PCg /BA 3a
		7	0.966	3.47	3.14	0.001	18 -31 4	R Thalamus (temporal)
		9	0.975	3.43	3.11	0.001	9 44 -17	R Orbital/Rectal g
		10	0.989	3.31	3.01	0.001	57 -55 19	R MTG
		4	0.99	3.3	3.01	0.001	57 8 16	R IFG (P. Operularis)

Abbreviations: Occ: Occipital, g: gyrus, MOg: Middle Occipital gyrus, IOg: Inferior Occipital gyrus, ITG: Inferior Temporal gyrus, IFG Inferior Frontal gyrus P. Triangularis: Pars triangularis, IPL: Inferior Parietal Lobule, SPL: Superior Parietal Lobule, P. Orbitalis: Pars Orbitalis, POr g: posterior orbital gyrus, SOg: Superior Occipital gyrus, PCg: Post Central gyrus, STG: Superior Temporal Gyrus, MTG Medial Temporal Gyurs, MOg: Middle Occipital Gyrus, SMG Supra Marginal gyrus, ACC: Anterior Cingulate cortex, IOg: Inferior Occipital gyrus, PCC: posterior cingulate cortex

Beyond these regions there was activation in the fusiform and lingual gyri bilaterally, in the right post central gyrus, and in the right perirhinal cortex bordering anteriorly on the parahippocampal gyrus.

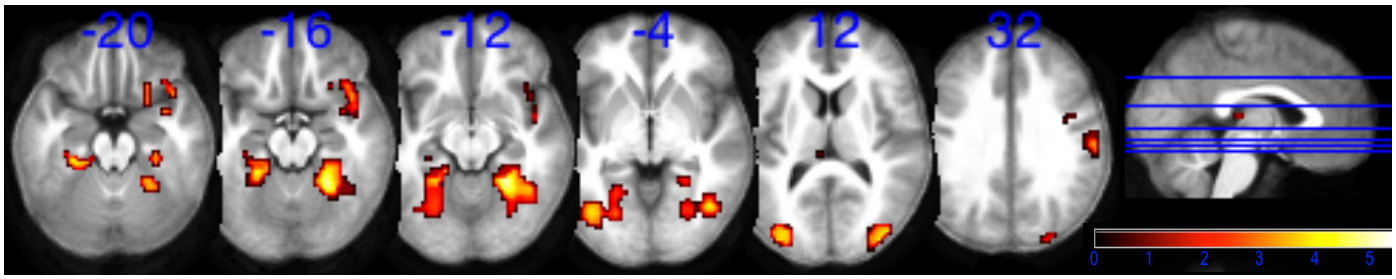

Figure 2.13. fMRI activations to Novelty outside the primary ROI network. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p<0.005

For the reverse contrast, corresponding to cue familiarity, there was bilateral activation in the precuneus (table 2.3 figure 2.14).

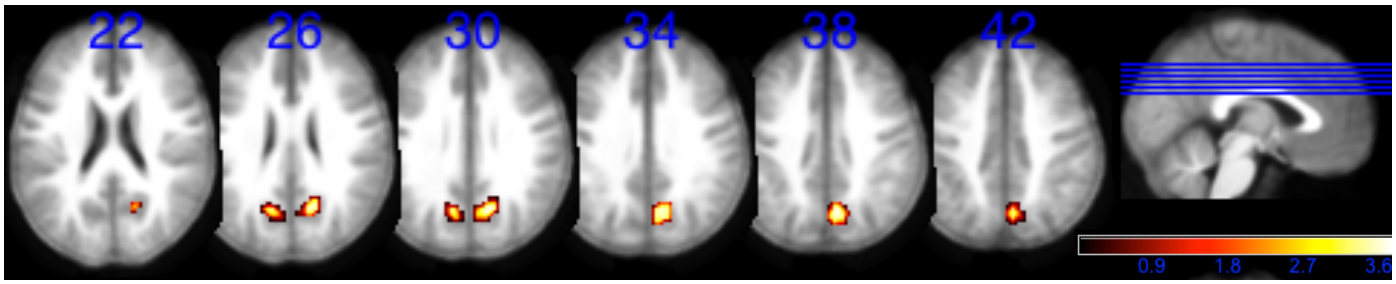

Figure 2.14. fMRI activations to Novelty<Familiarity in the whole brain. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p<0.005

2.6.2.3 Emotion

For the main contrast of emotion (all emotional cues greater than neutral cues) within the primary ROI network there were large activations in the amygdalae bilaterally extending to anterior hippocampal regions, and in posterior hippocampal regions (table2.3 figure 2.15). There were also clusters of activation within the midbrain both ventrally within the SN/VTA

mask and dorsally approximating the location of the periaqueductal grey and superior colliculi.

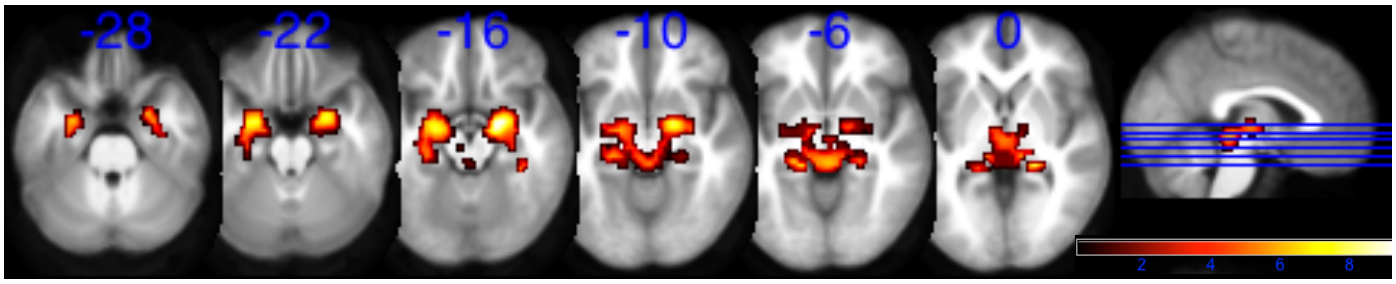

Figure 2.15. fMRI activations to Emotion within the primary ROI network. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p<0.005

Outside the primary ROI network there was activation in the inferior frontal gyri bilaterally, extending to the dorsolateral prefrontal and medial superior frontal cortex, ventromedial cortex, and in large lateral occipital regions extending ventrally to the fusiform and lingual gyri, and dorsally to the precuneus and cuneus (table 2.3 figure 2.15).

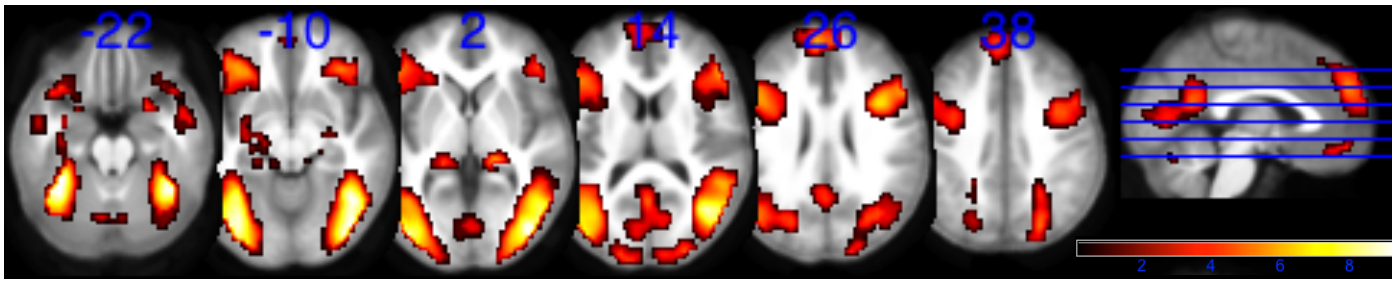

Figure 2.15. fMRI activations to Emotion outside the primary ROI network. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p<0.005

For the reverse contrast (neutral cues greater than emotional cues) there was bilateral activation in the ventral striatum, and in posterior hippocampal and adjacent parahippocampal regions (table 2.3 figure 2.16). Outside this primary ROI network there was activation in the anterior cingulate cortex, the right middle and inferior frontal gyrus, and in the right dorsolateral prefrontal cortex (table 2.3 figure 2.17).

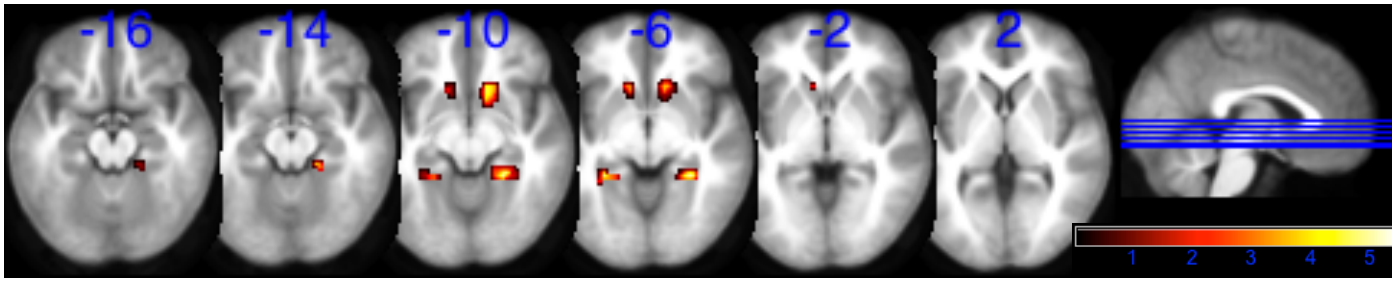

Figure 2.16. fMRI activations to Emotion <Neutral cues within the primary ROI network. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p<0.005

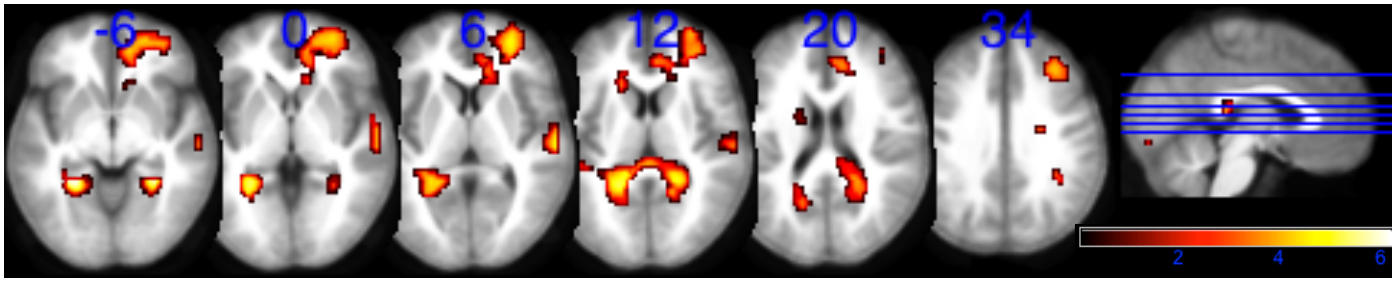

Figure 2.17. fMRI activations to Emotion <Neutral cues outside the primary ROI network. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p<0.005

2.6.2.4 Reward x Emotion

There were interactional effects between reward and emotion in the right amygdala, in bilateral posterior hippocampi and adjacent parahippocampal gyri, and in bilateral lingual and occipital gyri (table 2.3 figure 2.18). Plots of main areas of interaction are provided in figure 2.19.

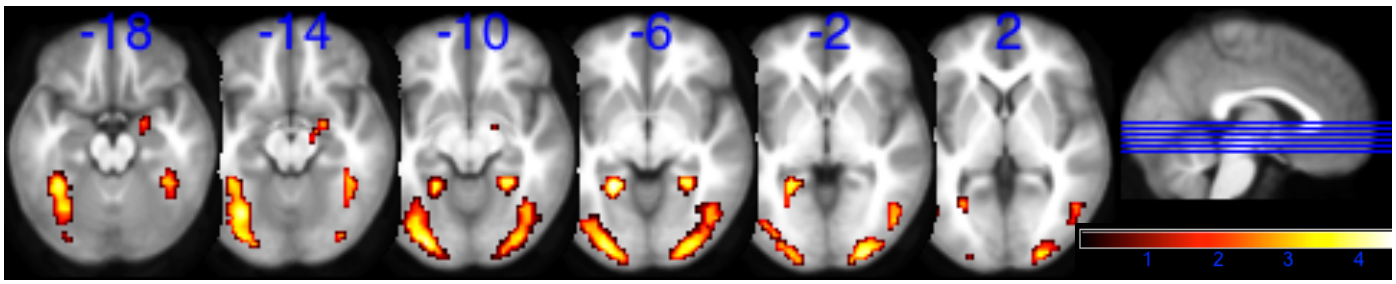

Figure 2.18. fMRI activations representing areas of Reward x Emotion interactions in the whole brain. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p<0.005

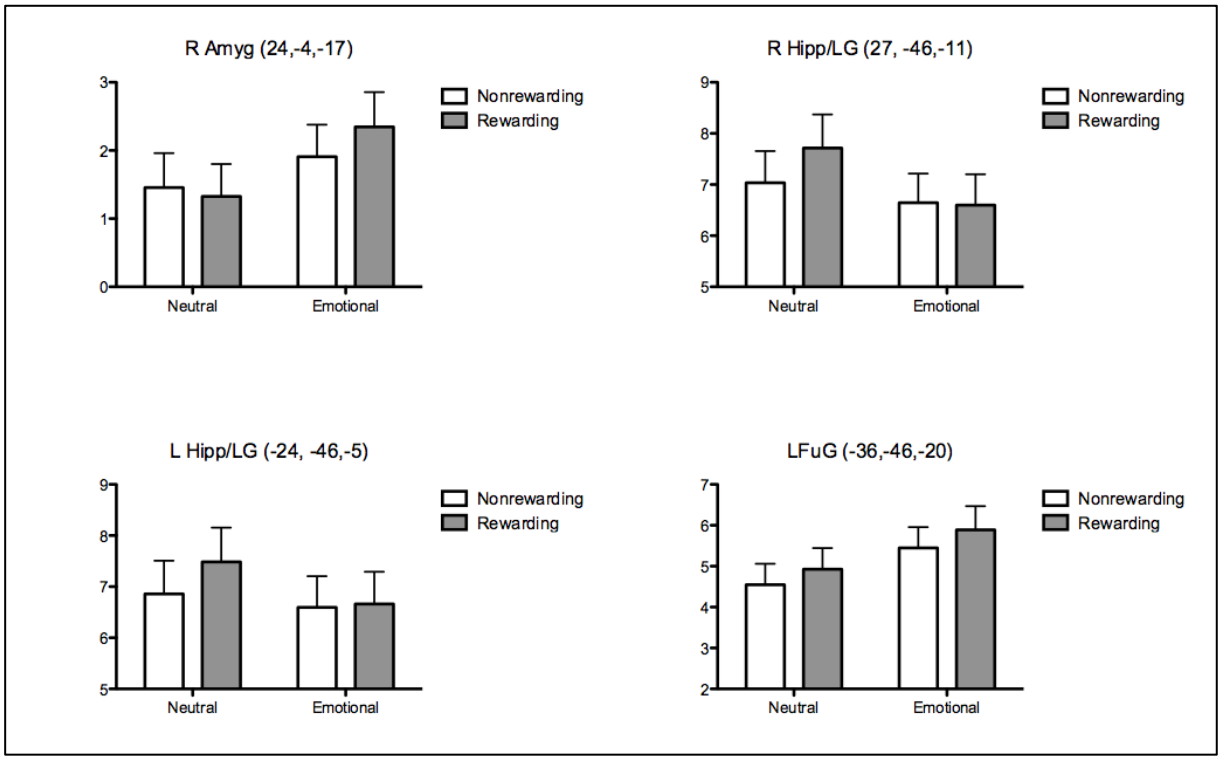

Figure 2.19 - Reward x Emotion interactions for selected activation clusters. Amyg: Amygdala; Hipp/LG: hippocampus/Lingual Gyrus; FuG Fusiform Gyrus

In the right amygdala-anterior hippocampus additional activation associated with rewarding stimuli was evident during emotional but not neutral trials, whereas in bilateral posterior hippocampal/PHG regions the reverse applied, with reward-related activation evident in neutral but not emotional trials. In the lingual/occipital regions the effects of emotion were greater in reward-predicting trials and vice versa.

2.6.2.5 Novelty x Emotion

There were interactional effects between novelty and emotion bilaterally in the ventral striatum, though these did not reach corrected significance levels. Outside the primary ROI network there were interactions in bilateral precuneus, frontal poles, the right DLPFC and in the occipital cortices including primary visual cortex (figure 2.20). In the ventral striatum and frontal areas the reduced activation associated with emotion was diminished during familiar

trials; similarly the activation associated with novelty in neutral trials was attenuated during emotional trials. In the occipital areas in the contrast the activation associated with emotion was enhanced with familiar trials (Figure 2.21).

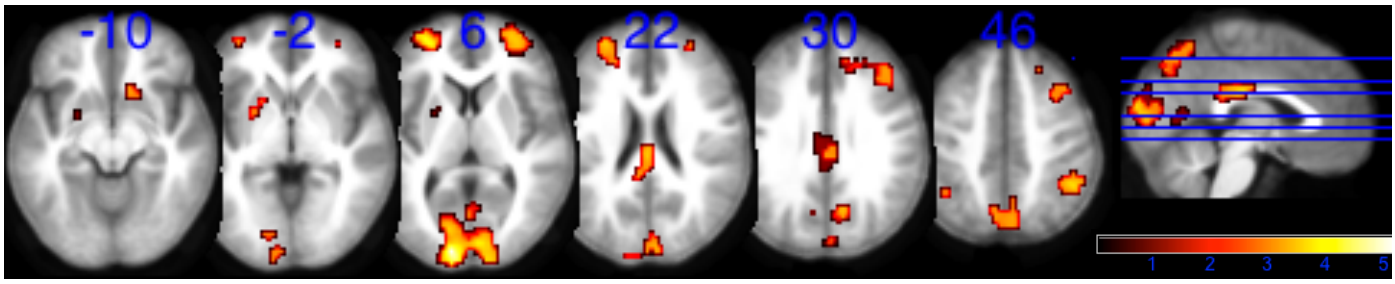

Figure 2.20 fMRI activations representing areas of Novelty x Emotion interactions in the whole brain. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p<0.005

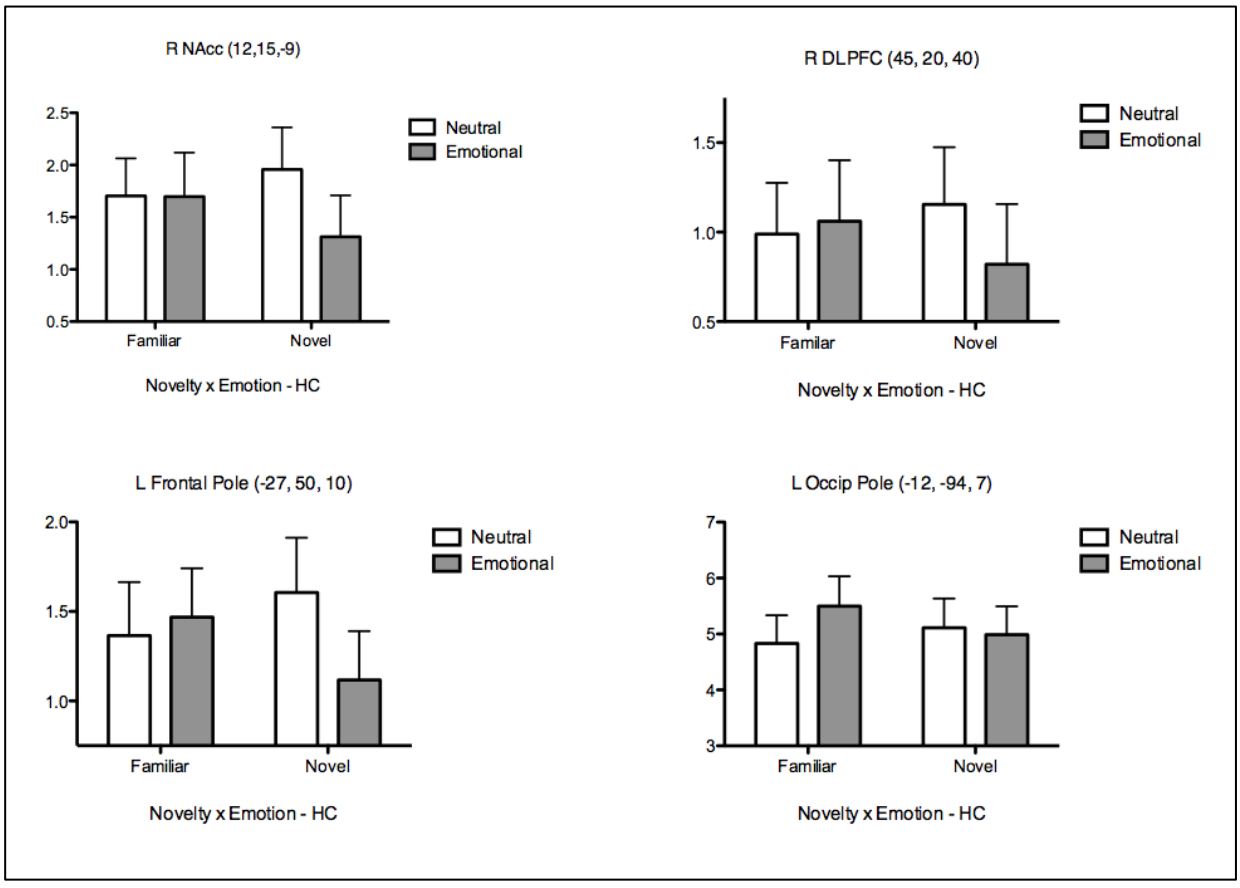

Figure 2.21 - Novelty x Emotion interaction plots for selected activation clusters. NAcc: Nucleus Accumbens, DLPFC: Dorsolateral Prefrontal Cortex, Occip: Occipital

2.6.2.6 Reward x Novelty

There was an interaction between activation associated with reward and novelty in an area centred in the anterior right hippocampus that extended to include the amygdala (figure 2.21), in a small area within the midbrain, and in the left mid-hippocampus. In these areas activations were additive (figure 2.22); positive responses to reward were present only in novel trials and vice versa. There were similar interactions in the fusiform gyri bilaterally and in the left orbitofrontal region.

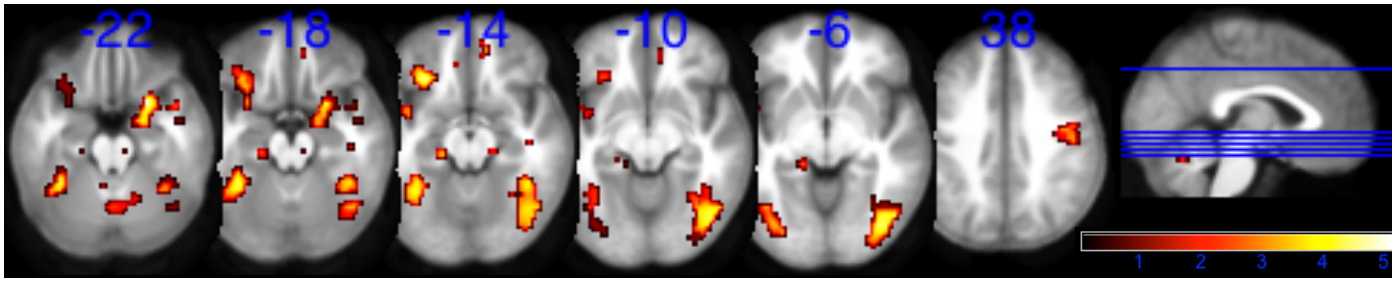

Figure 2.21 fMRI activations representing areas of Reward x Novelty interactions in the whole brain. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p<0.005

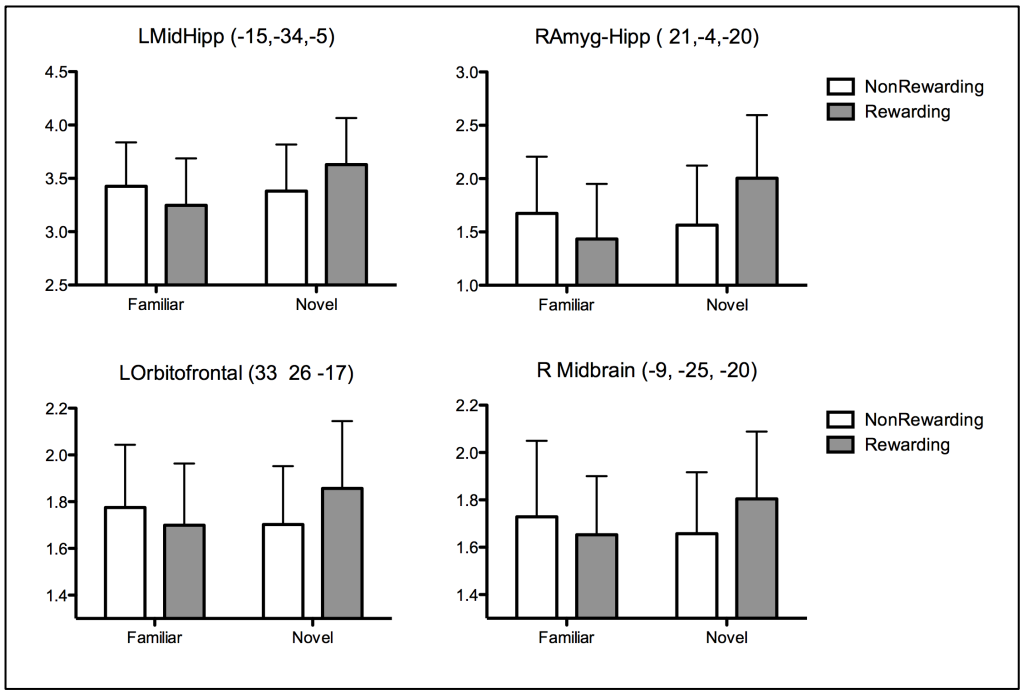

Figure 2.22 - Novelty x Reward interaction plots for selected activation clusters. Amyg: Amygdala, Hipp: Hippocampus, MidHipp: Middle hippocampus

2.7 Discussion

2.7.1 Summary of the main findings

In this study I measured behavioural and neurofunctional indices of healthy participants' reactions to 3 putatively salient aspects of visual scenes: reward anticipation, novelty, and negatively valenced emotional arousal. I used 2 behavioural indicators of salience processing: reaction time comprising attention, orientation, response selection and motor function, and recognition memory, comprising incidental encoding and consolidation. Activation was used as a proxy of neural function in preselected candidate structures and in the whole brain. I hypothesised that there would be significant behavioural and/or neurofunctional responses to each individual element and interactions between elements, suggestive of integration of salience processing.

I found behavioural and neurofunctional evidence for the contribution of each of the three factors, and for interactions between Reward and Emotion, and between Novelty and Emotion. I also found evidence for interactions between Reward and Novelty at a neurofunctional but not a behavioural level. These results support a broader conception of what constitutes salience and salience processing in the healthy brain.

2.7.2 Reward, Novelty and Emotion interact to affect behaviour

Broadly conceived, salient stimuli are stimuli that stand out relative to their context, arouse behavioural and cognitive responses, and may lead to cognitive changes, such as learning and new memories (Kapur, 2003; Li, 2002). Salience may be thus thought of as the 'common currency' amongst competing stimuli 'bidding' for limited cognitive resources (Redgrave, Prescott, & Gurney, 1999), including those involved in allocating attention and orientation, in

selecting response and action, and in learning, encoding and consolidating memories. My aim was to attempt to measure how much 'currency' reward, emotion and novelty had in a group of healthy control participants.

The SIT indexed behavioural responses to visual scenes with varied reward-predicting, novelty and emotional characteristics firstly in terms of reaction times, reflecting attention, orientation, visual processing, action selection and motor response, and secondly through delayed recognition memory at 1hour, reflecting encoding, and at 24hours, reflecting consolidation. Changes in reaction times and memory formations likely reflected incidental/passive processes, as participants were not told to speed their responses nor that there were be a later memory test. Key 'physical' salience attributes of visual cues (size, colour, luminance) were equivalent across categories, and the factorial design of the SIT ensured robust examination of main effects and interactions.

As hypothesized, there were significant deviations in both reaction time and delayed recognition to each tested element of salience, and significant 2 way interactions between elements. Participants were instructed to respond to all stimuli aside from the 2 'NoGo' cues, and reward did not depend on speed of response. Nevertheless, responses were slower for novel stimuli and emotional stimuli, and faster to reward predicting stimuli (excluding those with emotional content). Speed of response may be affected by several cognitive and motor components. For reward predicting stimuli it is likely that the cues (which were indoor scenes) became conditioned stimuli predicting later reward, and thus became attributed with increased 'incentive salience' (Berridge, 1998), or more broadly, *appetitive motivational salience*. The motivational aspect here emphasizes the spur to action *towards* the stimulus, leading to an overall speeding of response, although in this case it may have also incorporated increased attention, orientation, visual processing or other mechanisms. For negatively valenced emotional stimuli, there was a slowing of response, and the stimuli may be thought

of as similarly possessing motivational salience, but of opposite valence. Thus stimuli with *aversive motivational salience* similarly spur to action, but *away* from the stimulus, which may correspond to longer reaction times. It may also be that processing the emotional content required additional cognitive resources, leading to slowed responses. For novelty there was a slowing of response time, likely reflecting the speeding of the visual processing of scenes that had been seen before. Thus reaction time gives some important clues as to elements of salient stimuli, but is a composite measure (Posner, 2005).

These main effects were also evident when examining the impact of each element on recognition rates - emotion, familiarity and reward all boosted recognition hit rate and discrimination accuracy, supporting their salience in this respect. At 1hr reward also induced a large increase in false alarms that led to a reversal in the direction of hit rate effect on discrimination accuracy, rate whilst emotion reduced false alarm rates. At 24hours false alarms were reduced such that the discrimination accuracy was improved for reward, and further improved for emotion. Perhaps salient stimuli that increase both hit rate of memory but also false alarms, like reward, relate to the appetitive motivational salience of this category – participants *want* to remember these more, and so do, but often falsely. Conversely, scenes with aversive motivational salience (emotional scenes) had greater hit rate but reduced false alarms, and therefore greater discrimination accuracy. These remain speculative interpretations, and not easily testable in the current design. The need for pre-familiaristion limits interpretations of novelty on recognition.

Interestingly I found that emotion interacted with both reward and novelty on RT and recognition memory. Emotional scenes had a greater effect on slowing RT and boosting recognition hit rate and discrimination accuracy when familiar than when novel. In this respect prior exposure to scenes with emotional content sensitized later behavioural

responses. These interactions on recognition were also greater when tested at 24hr than at 1hr, further evidence of emotional responses evolving over time.

Emotion also affected behavioural responses to reward. In neutral trials reward anticipation sped responses, whilst in emotional trials this was reversed. Here perhaps the overall motivational salience was increased (spur towards action of one sort or another), but the net valence is aversive, so the net effect was of greater slowing. Alternatively, independent emotional processing may interfere with reward related processing more than other processes. In contrast the recognition boosting effects of reward were reduced in emotional trials, and vice versa. This may reflect the opposing motivational valence of these stimuli, but it also may reflect a performance ceiling reached in these doubly salient trials. Nevertheless there is consistent behavioural evidence of interaction of emotion with reward and with novelty, emphasizing the importance of affective context in salience processing.

2.7.3 Reward Novelty and Emotion activate a subcortical limbic network

During fMRI scanning of the SIT there were clear main effects of each salient element in relevant structures within the primary ROI network derived from the Lisman and Grace model (Lisman & Grace, 2005). This was particularly strong for emotion, which was associated with activation in the amygdalae, important in emotion processing (Costafreda, Brammer, David, & Fu, 2008), the hippocampi, relating to context and memory, and several areas within the midbrain. The latter were in both ventral regions approximating the SN/VTA, the major site of dopaminergic neurons, and also in more dorsal /caudal regions incorporating the locus coeruleus, a major site of noradrenergic neurons: previous work has demonstrated that both these transmitters are relevant for emotional responses in the human brain (Jabbi et al., 2012; Sara, 2009). The dorsal midbrain cluster also included the periaqueductal grey, which is responsive to aversive stimuli and has large inputs onto the SN/VTA, as well as the superior colliculi, which respond to spatial aspects of visual stimuli and may also code

novelty and other aspects of salience (Redgrave, Gurney, & Reynolds, 2008). These also have direct inputs to the SN/VTA (Comoli et al., 2003). Conversely, The ventral striatum was more activated by neutral than emotional stimuli, suggesting that in this region these pictures may have represented unexpected aversive stimuli, consistent with prediction error accounts of ventral striatal function (Schultz, 2010; Ungless, Argilli, & Bonci, 2010).

The exploratory whole brain analysis revealed additional activation in response to emotional stimuli in prefrontal areas such as the IFG/MFG, OFC and VMPFC. The DLPFC and ACC were activated in the reverse contrast, and are known to play an important role in regulating emotional experiences and in modifying subcortical responses (Banks, Eddy, Angstadt, Nathan, & Phan, 2007) while the IFG, OFC and mPFC are involved in the appraisal and expression of emotional experiences (Etkin, Egner, & Kalisch, 2011; Jabbi & Keysers, 2008).

Novelty led to activation in the middle and posterior regions of the hippocampus bilaterally, consistent with its established role in context related calculations (Lisman & Grace, 2005), whilst the reverse contrast led to activation in the precuneus, known for its role in recognition (Dörfel et al., 2009). It is important to highlight that this was a true absolute 'novelty' effect as each stimulus was indeed new and different from the familiar stimuli, which themselves were different from one another. This is in contrast to similar effects sometimes conflated with novelty, such as 'rareness', 'deviance' or 'targetness' such as in oddball paradigms when contrasted against a repeated 'standard'. Unlike Bunzeck et al (2006) we did not see midbrain activation to absolute novelty, however this may reflect differences in task, MRI parameters and analysis, and there is a broad base of human and animal evidence of dopaminergic neurons' response to stimulus novelty (reviewed in Redgrave et al., 2008).

Reward anticipation, formed by contrasting the reward - relevant outdoor-indoor setting of each scene, led to activation in the midbrain, and in the inferior frontal and orbitofrontal gyri

bilaterally. This network of activation suggested that these reward predicting cues were indeed serving as conditioned stimuli for the expected later monetary reward. Interestingly however activations were not detected in the ventral striatum. This may be in part due to susceptibility artefact in this region adjacent to the nasal sinuses, which also would explain the somewhat lateralized orbitofrontal responses. We deliberately made the task responses irrelevant to reward, in order to avoid biasing towards this aspect of salience. It is likely that the reward probe is therefore weakened relative to paradigms that require accurate or speeded active responses to obtain reward (Zink, Pagnoni, Martin-Skurski, Chappelow, & Berns, 2004). An absence of ventral striatal activation to reward may also relate to incomplete switching of responses from outcome to reward predicting cue. Participants were informed of the reward contingencies prior to the scanning session, and performed a practice session where they experienced the reward contingencies and were given the money earned directly in cash. However as participants were not explicitly asked for a response indicating each trial's reward prediction it is not possible to accurately model this.

2.7.4 Salience responses in visual sensory cortices

In the secondary visual areas there were large activations to reward predicting stimuli that were otherwise equivalent in terms of basic physical visual characteristics. This was not expected, but may relate to suggestions by Redgrave and colleagues (Redgrave & Gurney, 2006), who point out that the short latency phasic dopamine signal (onset around 100ms) is too fast to reflect calculation of a prediction error as shown by Schultz (Schultz, 1997), which would necessarily require a saccade towards the stimulus (taking at least 200-300ms). They suggest instead that reward related calculations are encoded in sensory pathways, which project onto dopaminergic areas via for example the superior colliculi (Comoli et al., 2003). There was also large secondary visual cortex activations for aversive emotional stimuli, suggesting that this sensory representation may reflect salience in a broader sense. fMRI

timescales are too slow to investigate timing directly, but the findings in the visual cortices are nonetheless interesting in view of this model.

2.7.5 *Responses to Reward in the Amygdala and Hippocampus depend on Emotion*

Supporting the behavioural findings, there was evidence for interactions between reward, novelty and emotion that may suggest the neural location of these interactions. Interactions between reward and emotion were seen in the right amygdala and in the posterior hippocampus bilaterally. The anterior hippocampus and amygdala are intimately connected with other limbic structures, and hippocampal responses here are proposed to reflect the 'affective layering' of place or circumstance (Grace, 2010). Accordingly responses in this region to reward depended on emotional content and were absent in neutral trials. This interaction was similar in nature to that seen between reward and emotion at the behavioural level (on reaction time); perhaps this difference is in part due to greater amygdalar processing during rewarding emotional trials. In contrast, the posterior hippocampal region, which lacks limbic connections, responded to reward only in the absence of emotion; this interaction was again similar to that seen behaviourally for recognition, suggesting a role of this area in recognition.

In bilateral secondary visual areas we also found interactions between reward and emotion, which were additive, that is that reward responses here were increased for emotional scenes. This adds support to the speculation that salience may be represented here regardless of valence.

2.7.6 *Responses to Emotion in the Ventral Striatum and Prefrontal Cortex reduce with familiarity*

In the ventral striatum there was relative deactivation for novel emotional stimuli that diminished with familiarity, although when interpreting this interaction it should be

remembered that it did not meet corrected levels of significance. This supports the notion that this deactivation represents an unexpected aversive stimulus, consistent with a prediction error model of striatal signaling. A similar interaction was seen in the frontal poles and in the DLPFC, which may also reflect a mechanism of healthy emotional regulation with repeated presentation - familiar cues had been presented 3 times immediately prior to scanning. Connections from the prefrontal cortex are thought to play an important role in regulating limbic responses to emotion (Banks et al., 2007; Etkin et al., 2011) and may also involve neuromodulation via dopamine in the ventral striatum and amygdala (Kienast et al., 2008; Siessmeier et al., 2006). Notably however no such interaction was seen in the amygdala itself, which remained responsive for both novel and familiar emotional scenes. This habituation of responses contrasts with the behavioural sensitization seen to familiar emotional cues on both reaction time and recognition memory, and in the occipital cortex we see sensitization as well – activations to emotion seen here were present to familiar but not novel stimuli.

2.7.7 Reward and Novelty interact synergistically in the Amygdala and Hippocampus

Finally there were additive effects of Reward and Novelty in the anterior hippocampus and adjacent amygdala, as well as trends for additive effects in the midbrain and the left orbitofrontal cortex. Positive activations to reward and novelty in these regions were synergistic, supporting the notion that the 'novelty bonus' (Dayan, 1996; Kakade & Dayan, 2002) that motivates the search for additional rewards in new environments is instantiated in the hippocampus and its limbic connections, as well as in reward regions such as the midbrain and orbitofrontal cortex. Both reward and novelty are known to activate dopaminergic regions (Duzel et al., 2009) which send projections to limbic structures such as the hippocampus and amygdala, and which may underlie a mutual reinforcement effect of Reward and Novelty, which is predicted by the Grace model (Lisman & Grace, 2005). This resonates with findings

by Guitart-Masip et al (2010) who found a similar interaction in the ventral striatum and with other similar studies (Bunzeck, Doeller, Dolan, & Duzel, 2012; Krebs, Schott, Schutze, & Duzel, 2009b).

2.7.8 Limitations

Although the factorial event related design of the SIT allowed robust examination of the main and interactional effects of reward, novelty and emotion, it did so at some cost of power when compared to simpler block designs or single factor cognitive subtraction designs. This influenced the level of statistical significance and method of correction applied, and the interpretation of some of the findings therefore needs to be cautioned against the possibility of type I error. Set against this is the additional benefit that factorial designs offer against confounding effects and the flexibility of examining a range of interactions, which was important for testing the hypotheses about the interactions and integration of salient elements. The peak activations seen fell largely within the limited hypothesis driven network of primary ROIs from the Grace network model, or had well established roles in the respective effects examined.

A further difficulty was in titrating 'salience-equivalent' levels of each of the probes of reward novelty and emotion. A disparity between these levels may have accounted for the behavioural and neurofunctional effects being strongest for emotional salience, and weakest for reward. In order to avoid over-complicating a complex task, I did not measure reward prediction on each trial, and outcome did not depend on performance; both may have reduced the relative effect of reward. However robust main effects and interactions were seen to each of the probes lending support to the validity of the task.

2.7.9 Conclusions

Salient stimuli 'pull' cognition and 'push' behaviour and are multifaceted. The salience of a stimulus in a particular context involves interactions between several factors related to its features, including reward, novelty and emotion. A diversity of cognitive processes and neural substrates may thus participate in salience processing, but the motivational 'common currency' involves a brain network comprising the midbrain, hippocampus, amygdala, ventral striatum, and the sensory cortices. The contribution of each dimension of salience and their potential interactions should be considered in future studies of salience processing.

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3. Salience processing and the risk of psychosis

3.1 Introduction

The previous chapter investigated the contribution of Reward, Novelty and Emotion to salience processing in healthy subjects. This demonstrated that each type of salience modified behavior, in terms of reaction time and later recognition, and during fMRI scanning activated elements of a network centered on the midbrain and medial temporal lobe. It also demonstrated significant behavioural and neurofunctional interaction between these elements, particularly with emotion, and suggested that these pointed towards an integration of salient elements in producing the affective and motivationally valenced experience of *salience*; a common currency with which stimuli compete for cognitive resources.

Alterations in salience processing are prominent in models of several neuropsychiatric disorders, including addiction, affective disorders and psychosis. In addiction, seeking and using the substance becomes *hyper*salient, to the exclusion of all else; while tolerance may develop to physiological effects of the drug, the incentive salience of the drug and drug related cues becomes sensitized (Robinson & Berridge, 2008). In depression, the perceptual and experiential field is putatively *hypo*salient, such that nothing is motivationally relevant, while in mania the opposite applies - the world is vivid and full of promise and excitement (Gelder & Ibor, 2000; Gradin et al., 2011; Kumar et al., 2008). In psychosis, salience processing is thought to be dysregulated, such that irrelevant stimuli catch attention and take on meaning to an extent that demands explanation, explanation that can take the form of bizarre delusions (Kapur, 2003). While this account chimes well with patient and clinician phenomenological accounts of the early phases of psychosis (Bowers & Freedman, 1966; Mishara, 2010), empirical studies are limited by their focus on reward salience (Heinz & Schlagenhauf, 2010), and by their inclusion of subjects who have already developed a frank

psychotic disorder and have been treated with antipsychotic medication. By this stage delusions and hallucinations are fully formed, following a prior period of delusional mood or 'trema' (Mishara, 2010) where 'senses are sharpened, and the world takes on personal significance' (Kapur, 2003). This period often occurs in late prodromal or At Risk Mental State (ARMS), prior to the onset of frank psychosis. Participants with an ARMS experience psychotic-like symptoms with a corresponding decrement in occupational and social function but are often unsure about their experiences and do not yet meet operational criteria for psychotic disorder (Yung & McGorry, 1996). They are usually naïve to treatment with antipsychotic medication (Yung et al., 1996). The absence of the potentially confounding effects of treatment with drugs that block dopamine receptors is particularly helpful in studies of salience, as the latter is thought to be critically dependent on dopamine function.

Reward salience studies in psychosis often demonstrate reductions in the reward-nonreward contrast in the ventral striatum, attributed either to a reduction in the response to reward, or an increase in the response to neutral stimuli (Heinz & Schlagenhauf, 2010); the latter is interpreted as evidence of aberrant salience in psychosis. The extent to which salience processing is altered in the ARMS is unknown. While many brain and cognitive abnormalities in the ARMS are qualitatively similar to those in psychosis, such as an increase in levels of striatal presynaptic dopamine synthesis (Howes et al., 2009) or a reduction in regional grey matter volumes (Mechelli et al., 2011), others such as an increase in pituitary volume (Yung, Phillips, et al., 2007b), show effects in the opposite direction, commensurate with a disease staging model that reflects dynamic changes with illness progression (L. J. Phillips et al., 2006; Wood, Yung, McGorry, & Pantelis, 2011).

ARMS subjects, who are symptomatic, but not yet psychotic, may show intermediate levels of salience dysregulation, and a commensurate decrease in measures of salient-nonsalient contrasts. Alternatively they may show heightened responses to salient stimuli, prior to a later

dysregulation in psychosis. This possibility resonates with patient and physician descriptions accounts of salient stimuli becoming more vivid and compelling, before being overwhelmed by irrelevant stimuli (Bowers & Freedman, 1966). This may be to salience generally or be to particular aspects. We previously demonstrated interactions between emotional processing and reward and novelty in a group of healthy controls using behavioural measures and fMRI (Chapter 2), and interpreted this as evidence towards an integration of these influences in salience processing. Alterations may be evident both with behavioural measures of salience, reaction time and delayed recognition rate, and with fMRI, particularly in the network of regions of interest derived from the grace model described in chapter 1, which overlapped with the regions activated in this task in controls.

Abnormalities in the reward domain are to be expected in this group, as these have consistently been evident in patients with psychosis. There may also be abnormalities in the emotional domain. Emotional processing is abnormal in psychosis and in the ARMS (Aleman & Kahn, 2005; L. K. Phillips & Seidman, 2008) and emotional disorders such as anxiety and depression are common in this period (Rosen, Miller, D'Andrea, Mcglashan, & Woods, 2006; Yung, Phillips, Yuen, & McGorry, 2004). Furthermore, the risk of transition to psychosis in high risk participants and community samples is increased if attenuated symptoms occur in the context of emotional dysfunction (Krabbendam & Germeys, 2005; Krabbendam & van Os, 2005; Yung, Buckby, et al., 2007a), and transition may be reduced by the active treatment of emotional disorders (Fusar-poli, Valmaggia, & McGuire, 2007).

In reality most stimuli have multiple aspects of salience, and it is unlikely that these would operate in isolation, and so interactions are expected. Indeed, it could be that it is not sufficient for a reward salience alone to be perturbed – it only matters if say emotional salience processing is also abnormal. As the strongest interactions in healthy controls were

between reward and emotion, and between novelty and emotion, we anticipated these would be most altered in ARMS participants.

I was also interested in a second network of regions that has recently been shown to respond to salient stimuli by facilitating a switch from default mode to central executive and task oriented modes (Seeley et al., 2007). In addition to the subcortical and limbic regions investigated so far, this network may also play an important role in salience processing. Alterations in this so-called 'salience network', comprising bilateral insulae and ACC, have recently been demonstrated in psychosis (White, Joseph, Francis, & Liddle, 2010), however this has not been investigated in ARMS participants.

The aim of the work in this chapter was to use the SIT to test the Reward, Novelty and Emotional elements of salience processing in unmedicated subjects with an ARMS. I predicted that relative to matched controls, ARMS participants would show altered behavioural and neurofunctional markers of reward, novelty and emotional salience processing, and altered interactions with emotion, but was agnostic as to the direction of these alterations. I predicted that the regions most relevant for these alterations were firstly in the network that responded to salience in controls comprising the midbrain, hippocampal formation, amygdala and ventral striatum, and secondly in the insula and ACC bilaterally.

3.2 Hypotheses

1. ARMS participants will show altered behavioural measures (reaction time and delayed recognition rate) to reward, novelty and emotional visual stimuli relative to healthy controls.

2. ARMS participants will show altered neurofunctional measures of reward, novelty and emotional salience processing relative to healthy controls in a network comprising the midbrain, ventral striatum/pallidum, amygdala and hippocampus.

3. ARMS participants will show altered neurofunctional measures of Reward Novelty and Emotional salience processing relative to healthy controls in the salience network, comprising the anterior cingulate cortex and bilateral insulae.

3.3 Methods

3.3.1 Recruitment

Participants were recruited from Outreach And Support in South London (Broome et al., 2005), a specialist service for the treatment of young people at high risk of psychosis. They were referred to OASIS by primary and secondary healthcare centres, schools, families and individuals could also self-refer. At intake they were assessed by a psychiatrist using the Comprehensive Assessment of At Risk Mental States (CAARMS Yung et al., 2005). Referrals were then discussed at the multidisciplinary team intake meeting and participants who met CAARMS criteria for an At Risk Mental State for Psychosis were then taken on by the OASIS service for treatment and follow-up for 3 years.

Following intake potential participants were asked by their clinical care coordinator if they would like to be contacted by the study researcher, who then made contact by telephone and described the procedures and aims of the study and provided written information sheets by post and/or email. Participants were given at least 48hours to consider their participation in the study, and it was stressed that a decision to participate would not affect ongoing treatment at OASIS. Twenty-nine healthy control participants were recruited by local advertisement and by 'word of mouth' (ARMS and control participants were asked to refer friends/peers) from the same geographic area of south east London to be as closely age, education, gender and ethnicity matched as possible. Matching of HC participants was also to a concurrently recruited third arm of the study, that of First Episode Psychosis participants (FEP), an older

group. Recruitment of HC participants was largely by word of mouth from ARMS and other HC participants' friends and social contacts, and in a minority of cases by local advertisement.

Written informed consent was obtained, and the study protocol was approved by the Hammersmith Research Ethics Committee.

3.3.2 Power calculation

Although the SIT fMRI paradigm has not been tested in subjects with an ARMS before, similar studies of reward, novelty and emotion have yielded significant results in healthy controls with group sizes of n=14 (Bunzeck & Duzel, 2006) and n=24 (Krebs, Schott, & Duzel, 2009). When working memory tasks have been used in the ARMS differences in activation relative to controls have been evident in groups of n=17 (Broome et al., 2009) while reward anticipation paradigms in first episode psychosis subjects have detected group differences with samples of 10-13 (Juckel et al., 2006; Murray, Lappin, & Di Forti, 2008); in these a larger effect size may be anticipated than in ARMS participants. A different paradigm from the same group using ARMS subjects versus controls accessing subcortical structures yielded a mean group difference of 0.39, SD 0.45, giving an effect size of d=0.87 (Roiser, personal communication). Using power calculations based on these estimates (G*Power 3.1 Faul, Erdfelder, & Lang, 2007) gives 90% power to detect a significant difference ($p<0.05$) with equal group sizes of 29 (figure 3.1a, 3.1b).

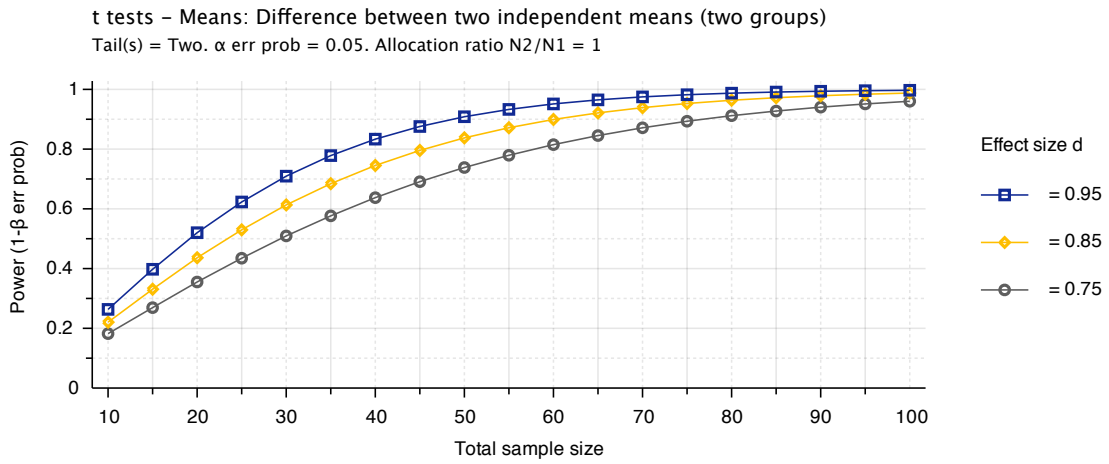


Figure 3.1a Power by total sample size for effect sizes 0.75-0.95

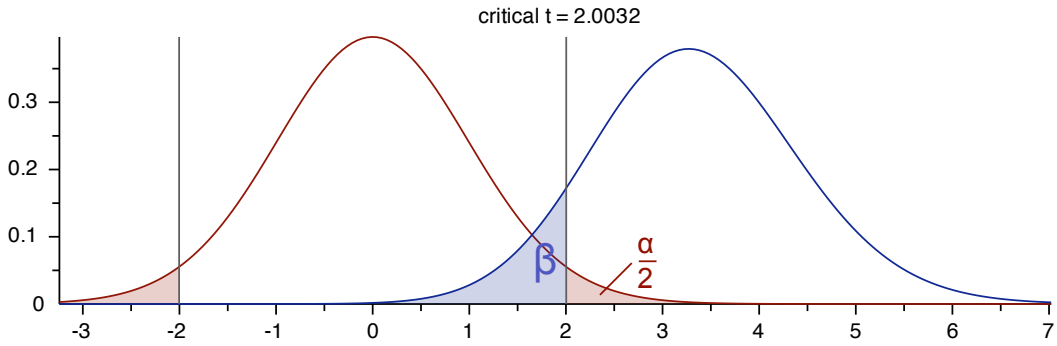


Figure 3.1b critical t values for 2-tailed independent samples t-test at α=0.05, β=0.1

3.3.3 Clinical measures

All participants underwent a structured clinical interview with the same clinician (TWB) covering from which a number of scales were scored: the CAARMS-positive scale (Yung et al., 2005), Hamilton-Anxiety scale (Hamilton, 1959), Hamilton-Depression scale (Hamilton, 1960) and Global Assessment of Function (GAF). Additionally participants filled in a number of self report questionnaires, the Temperament and Character Inventory (TCI Cloninger, 1994), Schizotypal Personality Questionnaire-Brief (SPQ-B Raine & Benishay, 1995) and Peters Delusional Inventory (PDI Peters, Joseph, Day, & Garety, 2004).

3.3.4 Behavioural

Methods for analyzing reaction time and recognition rate differences within the ARMS groups were as described in chapter 2.5.3. In order to perform between group comparisons an additional factor of group was added as a between subject variable in the ANOVA performed in SPSS v 17. Group average differences were calculated in order to determine the direction and size of effect.

3.3.5 fMRI

Similarly, fMRI analyses were performed within the ARMS group as in chapter 2.5.4**.** For between group comparisons, a 2-sample t-test was performed at the 2nd (group) level for each of the main effects and interactions of interest. As in chapter 2.5.3 we performed whole brain analyses at an uncorrected threshold of $p<0.005$ and applied Small Volume Correction for our pre-specified regions of interest. For visualization, fMRI activation maps display whole brain activations at $p<0.005$ uncorrected overlaid on average T1 weighted scans of all participants. I report both uncorrected and FWE_{ROI} corrected peak voxel significance and location, cluster volumes, and t and z values. Peak voxel location was determined using a probabilistic atlas tool (Tzourio-Mazoyer et al., 2002) and confirmed manually using the reference atlas of Mai et al (2008; Mai, Paxinos, & Voss, 2008).

3.4 Results

3.4.1 Participants

The demographic characteristics of ARMS participants and healthy controls are shown in table 3.1. There were no differences between ARMS participants and controls in premorbid IQ as estimated by the National Adult Reading Test (NART). ARMS subjects were on average 2.5 years younger than controls, and had 0.7 years less education than controls.

Demographic Characteristics

	ARMS	HC	Statistic (t/ χ^2)/Significance (p)
Number of participants	29	29	-
Mean Age -Mean(SD)	21.2 (3.1)	23.7 (4.3)	2.68/ 0.01*
Gender (F/M)	16/13	13/16	0.621/ 0.73
Ethnicity (BME/WB)	13/16	10/19	0.648/0.592
Years Education - Mean(SD)	11.9(1.2)	12.6(8.1)	2.7 /0.01*
Premorbid IQ (NART) -Mean(SD)	110(9.5)	114(11.4)	1.241/0.22
Handedness (R/L)	25/4	25/4	0.056/0.812

Table 3.1 - Demographic characteristics of ARMS and HC participants. BME: Black and Minority Ethnicity, WB: Any White background, IQ Intelligence Quotient, NART: National Adult Reading Test.

3.4.2 Clinical scales

Clinical scale scores are presented in table 3.2**.** As expected ARMS subjects scored significantly higher on CAARMS positive scales, Hamilton-Anxiety (Ham-A) and Hamilton-Depression (Ham-D) and Schizoptypyal Personality Brief Questionnaire (SPQ-B) scales, and lower on GAF scores.

Clinical Characteristics

Scale	ARMS	HC	Statistic (t)/Significance (p)
CAARMS-pos mean(SD)	7.8(3.8)	0.2 (0.6)	7.25/ <0.0001
Ham-A - mean(SD)	13.9(2.1)	0.5 (0.8)	7.88/ <0.0001
Ham-D - mean(SD)	15.0(7.4)	1.8 (2.4)	8.97/ <0.0001
SPQ-B - mean(SD)	13.3(3.8)	4.6 (4.5)	7.43/ <0.0001
PDI - mean(SD)	71.1(41.2)	25.7 (24.5)	4.90/ <0.0001
GAF - mean(SD)	54.9(6.6)	81.9(10.7)	7.76/ <0.0001

Table 3.2 - Clinical characteristics of ARMS and HC participants. CAARMS: Comprehensive Assessment of AT Risk Mental States; Ham-A: Hamilton Anxiety Rating Scale; Ham-D: Hamilton Depression Rating Scale; SPQ-B: Schizotypal Personality Questionnaire, Brief version; PDI: Peters Delusional Index; GAF: Global Assessment of Function

3.4.3 Compliance with tasks

Similar to control participants, ARMS participants complied well with the online SIT and delayed recognition tasks (table 3.3). During the practice SIT reward contingencies were explained and all participants completed 10 consecutive correct trials within 3 minutes and were given the money earned in cash. There were no significant differences between groups on task performance. In behavioural and fMRI analyses, error trials were excluded from analysis.

Task Compliance

Task	ARMS errors (%)	HC errors (%)	Statistic (t)/Significance (p)
SIT - Go trials	6.7 (12.5)	4.0 (5.9)	1.0 / 0.318
SIT - NoGo trials	13.5 (17.6)	10.2 (10.3)	0.98/ 0.333
Recognition 1hr	6.3 (5.2)	5.3 (4.2)	0.819/ 0.417
Recognition 24hr	5.5 (7.0)	3.6 (3.8)	1.355/ 0.183

Table 3.3 - Task Compliance during SIT and Recognition tasks of ARMS and HC participants.

3.4.4 Behavioural group comparison

For group comparisons of reaction time and recognition at 1hour and at 24hours we conducted repeated measures ANOVAs with reward, novelty and emotion as within-subject variables, and group entered as a between subject variable.

3.4.4.1 Reaction Time

The mean reaction time was 606.1ms; there was no difference overall between groups. ARMS participants had greater influences of reward, novelty and emotion on altering reaction time than controls, but these differences did not reach significance (figure 3.2). There were no significant group differences in reaction time related to 2-way interactions of these effects.

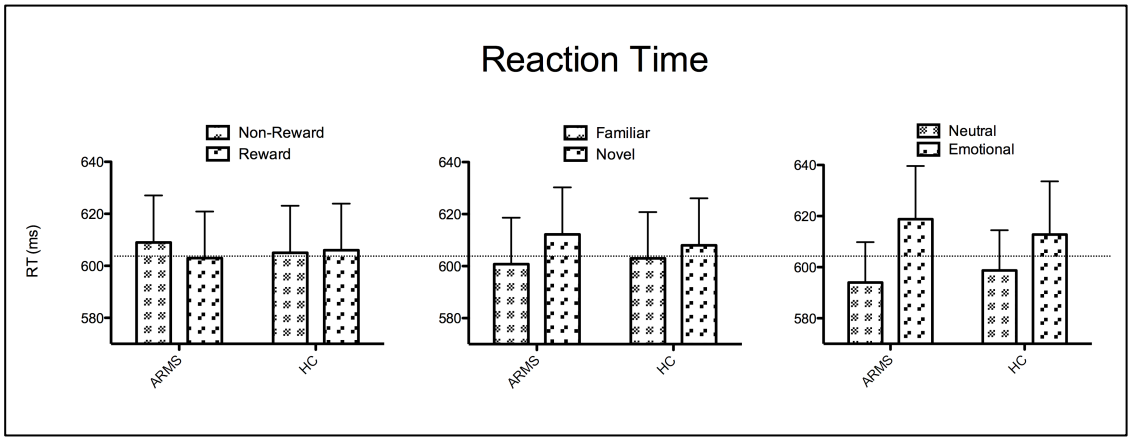


Figure 3.2 Reaction times to Main Effects of Reward Novelty and Emotion in ARMS and HC. Columns represent means, bars represent Standard Errors. Dotted line represents overall mean RT.

3.4.4.2 Recognition

Overall group differences in recognition rates collapsed across conditions and sessions are presented in table 3.4. ARMS participants had significantly lower overall hit rates (% old cues correctly recognised as old, HR), which when adjusted for false alarms (% new cues falsely recognised as old, FA) gave discrimination accuracies (hit rate adjusted for false alarms, DA) that were not significantly different. There were no differences between groups in overall false alarm rates.

Overall Recognition rates

	ARMS	HC	Statistic (t)/ significance (p)
Hit Rate %(SD)	52.3 (14.7)	60.3(9.9)	-2.424 / 0.019*
False Alarm Rate % (SD)	30.6 (16.0)	33.8 (12.7)	-0.645/0.522
Discrimination Accuracy % (SD)	21.7 (12.7)	26.4 (9.6)	-1.597/0.116

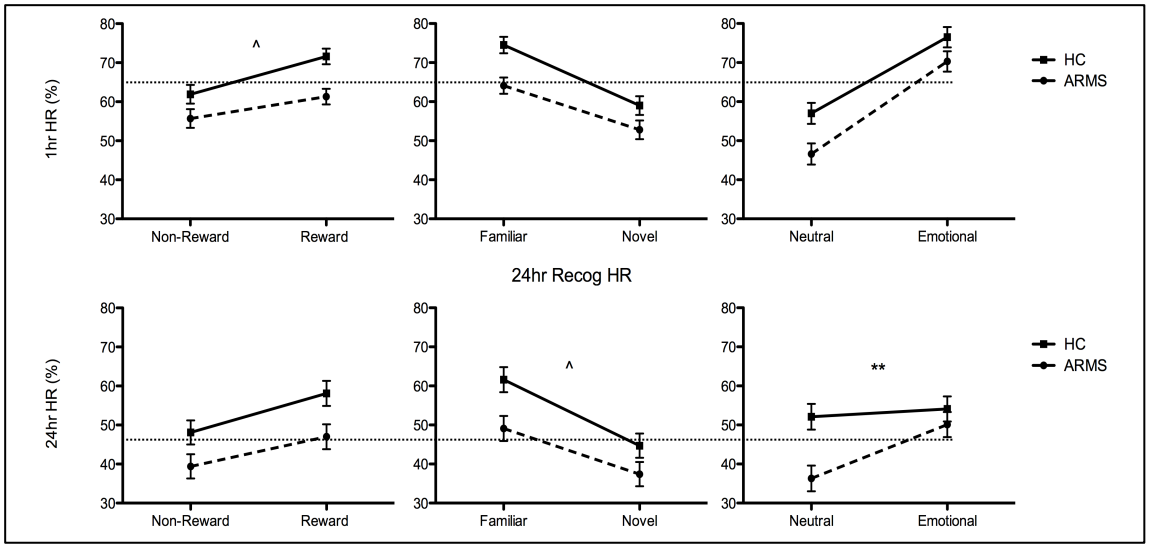
Table 3.4 - Overall Recognition rates in ARMS and HC participants

Main Effects

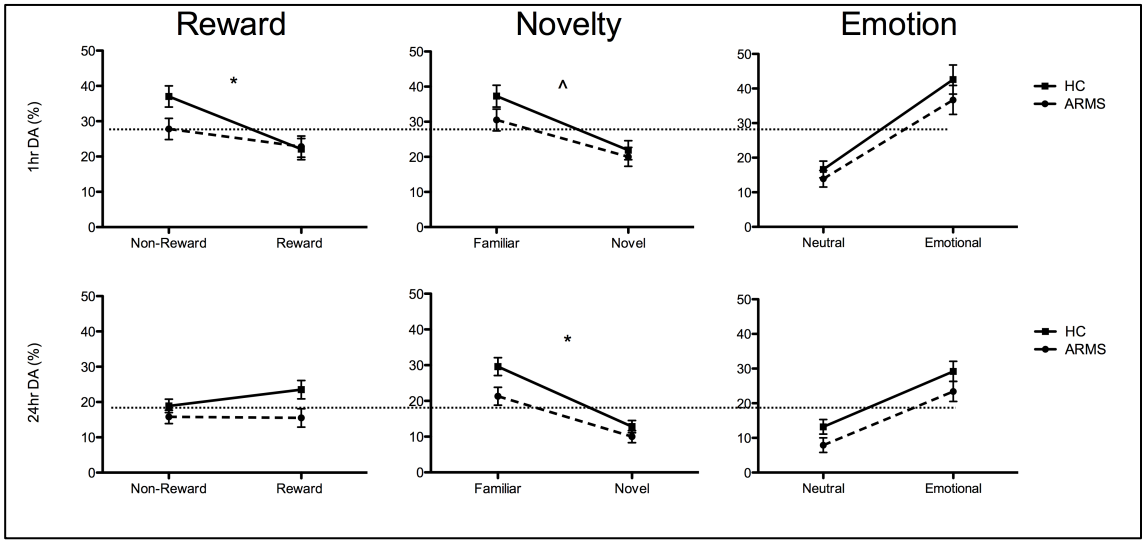
At 1hour the overall mean correct recognition hit rate was 62.6% (SD1.5). There was a trend towards an interaction of group and reward ($F(1,56)=3.163$, $p=0.081$); reward improved hit rates in both groups, but more so in controls (mean reward-nonreward group difference HC-ARMS 4.1% figure 3.3a). However reward also induced a greater increase in false alarms in controls ($F(1,56)=15.6$ $p<0.0001$, figure 3.3c) such that there was a greater reduction in 1hr discrimination accuracy due to reward in this group (mean reward-nonreward group difference HC-ARMS 9.9% $F(1,56)=7.936$ $p=0.007$, figure 3.3b) and discrimination rates for reward –predicting cues were similar in both groups. There was also a trend to a greater effect of familiarity in improving discrimination accuracy in controls ($F(1,56)=3.49$ $p=0.067$ figure 3.3b).

At 24hours the overall mean hit rate was 48.2%. There was now no difference on the effect of reward between groups, but there was a greater effect of emotion in the ARMS group (mean emotion-neutral related group difference HC-ARMS -11.8% $F(28,1)=2.84$ $p=0.003$, figure 3.3a), such that the hit rate for emotional cues was similar between groups (figure 3.3a). There was also a trend to a lesser effect of novelty in the ARMS group (mean familiar-novelty group difference HC-ARMS +5.2% $F(1,28)=3.715$ $p=0.059$). False alarms to emotional cues were reduced to a greater extent in controls at 24hr ($F(1,56)=7.936$ $p=0.007$), and so changes in 24hr discrimination accuracy due to emotion were equivalent between groups. The only significant group difference was in the novelty-familiarity contrast on 24hr discrimination accuracy; prefamiliarised cues were discriminated better by controls than ARMS participants.

A. Hit Rate



B. Discrimination Accuracy



C. False Alarms

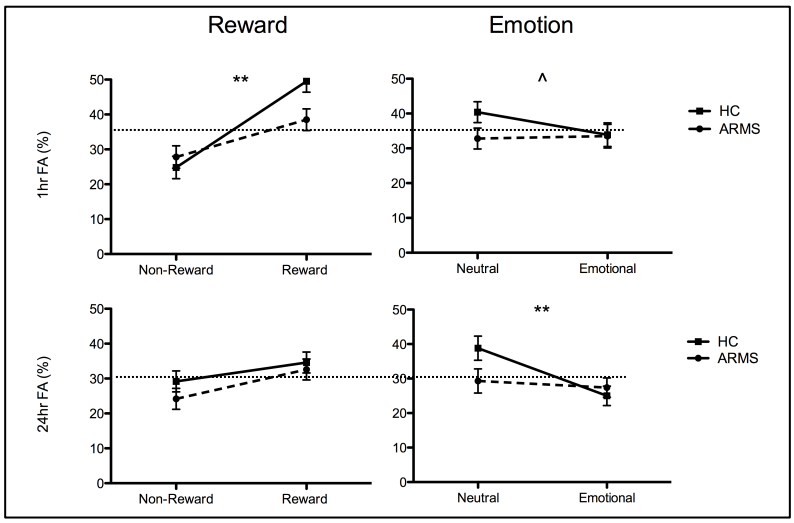


Figure 3.3
Mean (SD) A) recognition hit rate (HR), B) discrimination accuracy (DA) and C) false alarms (FA) for the main effects of Reward Novelty and Emotion, at 1hr and at 24hr in ARMS and HC groups. Dotted lines represent overall session mean rate, the slope of the line away from this horizontal mean reflects the influence of that factor on the specified outcome. Hit rate refers to % old cues correctly recognised as old, false alarms refers to % new cues falsely recognised as old, discrimination accuracy refers to hit rate adjusted for false alarm rate. *p<0.05 **p<0.01 ***p<0.001

Interactions

Group differences in 2way interactions were minimal. At 1hr there was a trend to an interaction on hit rate between group and the 2way interaction of reward and emotion ($F(1,56)=3.45$ $p=0.068$); in control subjects the effects of reward were greater in emotional trials than neutral trials whereas in ARMS this was not the case. At 24hr this trend persisted ($F(1,28)=3.615$ $p=0.062$), but when corrected for false alarms there was no significant group x 2way discrimination accuracy interactions at either time point. There were no group differences in interactions between novelty and emotion or between reward and novelty.

3.4.5 fMRI group comparison

3.4.5.1 Reward

Within the primary ROIs, ARMS participants showed greater activation to reward predicting cues than controls in bilateral clusters centered on the ventral pallidum bilaterally extending to included the left midbrain, and in the posterior right hippocampus (figure 3.7 table 3.5).

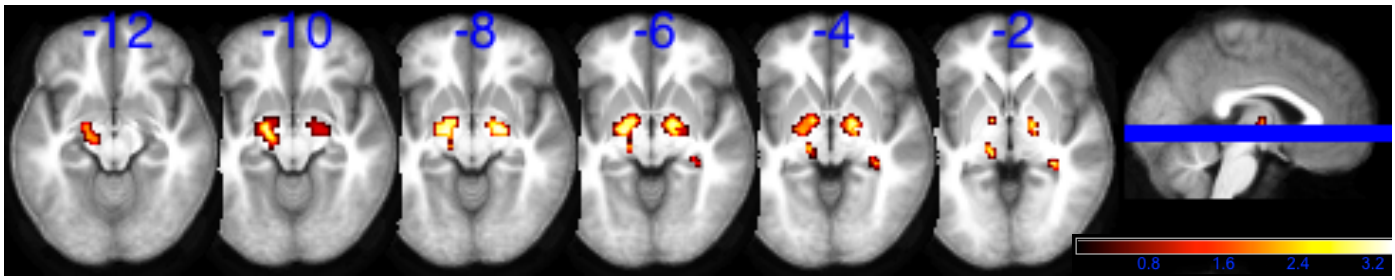


Figure 3.7 fMRI activations to Reward in ARMS greater than HC within the primary ROI network. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected $p<0.005$

These clusters of differential activation extended outside the primary ROI network into the left thalamus, and there was also activation in the right temporal pole bordering on the amygdala, in the posterior middle temporal gyrus, and in a small cluster in the left rectal gyrus

(figure 3.8 table 3.5). There were no areas where control participants activated more than ARMS participants.

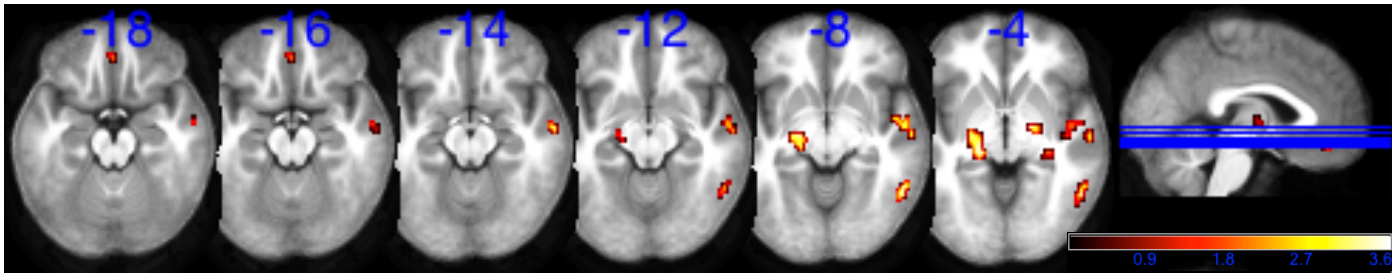


Figure 3.8 fMRI activations to Reward in ARMS greater than HC outside the primary ROI network. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p<0.005

3.4.5.2 Novelty

Within the primary ROI network there were no group differences in activation related to novelty. However, outside these regions there were areas of greater activation in controls than ARMS participants in bilateral low midbrain clusters and adjacent midline clusters in the cerebellum and adjacent parahippocampal/lingual gyrus, and in the precuneus (table 3.6), though none of these differences reached corrected statistical significance. There were no areas where ARMS activated greater than control participants.

3.4.5.3 Emotion

There were no differences between groups in the primary ROIs (table 3.5). Outside these, ARMS participants showed greater activation than controls related to emotional cues in a small cluster of the left lingual gyrus and less activation than controls in a small cluster of the right post central gyrus and the left orbitofrontal gyrus (table 3.6), though none of these differences reached corrected statistical significance.

ARMS v HC SIT task – Primary ROI Analysis

Contrast	+/-	cluster size k	p(FWE $_{WB}$)	p(FWE $_{ROI}$)	t	z	p(unc)	x,y,z (MNI)	Location
Reward	ARMS>HC	31	0.55	0.044	3.57	3.37	<0.001	18 -7 -5	R vPallidum
		53	0.633	0.066	3.47	3.28	0.001	-18 -13 -8	L vPallidum
		4	0.936	0.054	3.01	2.88	0.002	-15 -16 -11	L Midbrain
		5	0.959	0.275	2.91	2.79	0.003	33 -34 -2	R Hipp(CA)
	ARMS<HC	NIL							
Novelty	ARMS>HC	NIL							
	ARMS<HC	NIL							
Emotion	ARMS>HC	NIL							
	ARMS<HC	NIL							
RxE		10	0.975	0.276	2.87	2.76	0.003	-6 -7 -5	L vPallidum
				0.241	2.8	2.7	0.003	-9 2 -5	L NAcc
NxE		NIL							
RxN		28	0.359	0.095	3.16	3.02	0.001	0 -10 -5	Midbrain

Table 3.5 List of fMRI BOLD associated activations to main effects and interactions in ARMS vs healthy controls within the primary ROI network. Amyg: Amygdala, Hipp: Hippocampus, CA Cornu Ammonis, Cb: cerebellum, vPallidum: ventral pallidum, NAcc: Nucleus Accumbens

ARMS v HC SIT task – Whole brain analysis

Contrast	+/-	cluster size k	p(FWE $_{WB}$)	t	z	p(unc)	x,y,z (MNI)	Location
Reward	ARMS>HC	57	0.449	3.69	3.47	<0.001	-18 -28 -2	L Thalamus
		58	0.559	3.55	3.36	<0.001	39 5 -29	R Amyg (LB)
			0.722	3.36	3.19	0.001	48 -4 -29	R MTG
			0.953	2.93	2.82	0.002	36 -7 -26	R Hipp
		27	0.616	3.49	3.3	<0.001	54 -58 -5	R ITG
		38	0.833	3.2	3.05	0.001	57 -7 -11	R STG
		3	0.973	2.84	2.73	0.003	-3 41 -17	L Rectal g
	ARMS<HC	NIL						
Novelty	ARMS>HC	NIL						
	ARMS<HC	39	0.762	3.37	3.2	0.001	3 -73 4	L Lingual g
			0.975	2.91	2.8	0.003	0 -67 13	L Calcarine g
		104	0.826	3.28	3.12	0.001	6 -40 -14	Cb vermis
			0.94	3.06	2.92	0.002	21 -43 -14	R Fusiform g
			0.943	3.05	2.91	0.002	12 -43 -5	R Lingual g
		27	0.847	3.25	3.1	0.001	-9 -31 -26	L Midbrain
		12	0.866	3.22	3.07	0.001	12 -25 -26	R Midbrain
		5	0.98	2.88	2.77	0.003	30 -31 -20	R Fusiform g
Emotion	ARMS>HC	17	0.948	3.16	3.01	0.001	-27 -49 -5	L Lingual g
	ARMS<HC	11	0.854	3.36	3.19	0.001	51 -13 28	R PoC g
		3	0.997	2.79	2.69	0.004	-39 50 -8	L MOrb g
RxE		196	0.471	3.69	3.47	<0.001	-36 -34 25	L Insula
		133	0.486	3.68	3.46	<0.001	6 32 7	R ACC
		120	0.629	3.51	3.32	<0.001	-33 14 10	L Insula
		108	0.791	3.3	3.14	0.001	45 -1 4	R Insula
		15	0.825	3.25	3.1	0.001	12 59 -2	R MOrb g
		63	0.893	3.13	2.99	0.001	-30 -61 4	L Calcarine g
NxE		19	0.662	3.52	3.33	<0.001	36 14 10	R Insula
		4	0.99	2.82	2.72	0.003	42 8 -32	R Temp pole
RxN		24	0.958	3.06	2.93	0.002	30 32 -8	R IFG

Table 3.6 List of fMRI BOLD associated activations to main effects and interactions in ARMS vs healthy controls outside the primary ROI network. Amyg: Amygdala, Hipp: Hippocampus, MTG Middle temporal gyrus, ITG Superior Temporal Gyrus, STG, Superior Temporal Gyrus, Cb Cerebellum, PoCg Posterior Central gyrus

3.4.5.4 Reward x Emotion

There was a difference between ARMS and control participants in the in the interaction between reward and emotion in the left ventral striatum though this did not reach corrected statistical significance (figure 3.12, 3.13, table 3.5). There was a similar interaction in regions bilateral insulae and ACC (figure 3.14). In these regions ARMS participants showed significantly greater activations for reward in the context of emotion (figure 3.13, 3.15).

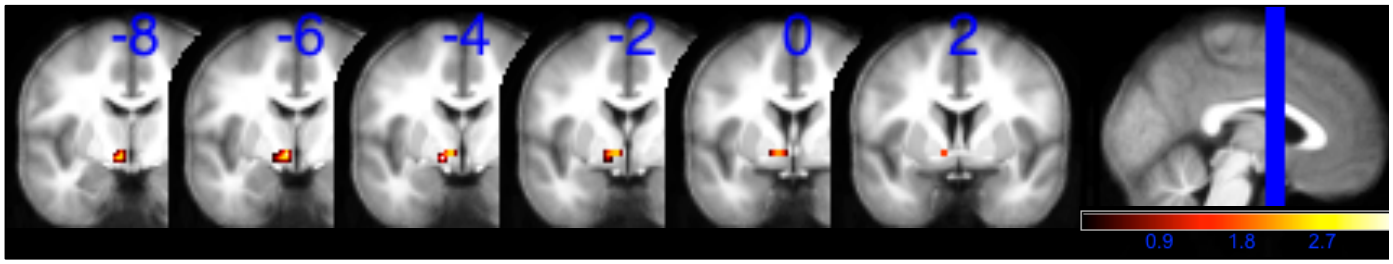


Figure 3.12 fMRI Interactions between Reward and Emotion in HC vARMS participants within the primary ROI network. Z coordinates ar displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p< 0.005.

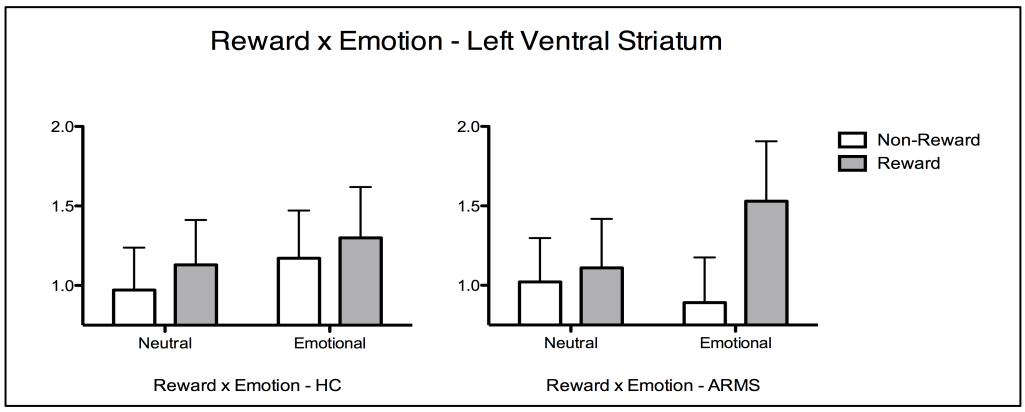


Figure 3.13 Reward x Emotion Interactions in L Ventral Striatum in ARMS v HC. Columns show mean activation +/- SEM

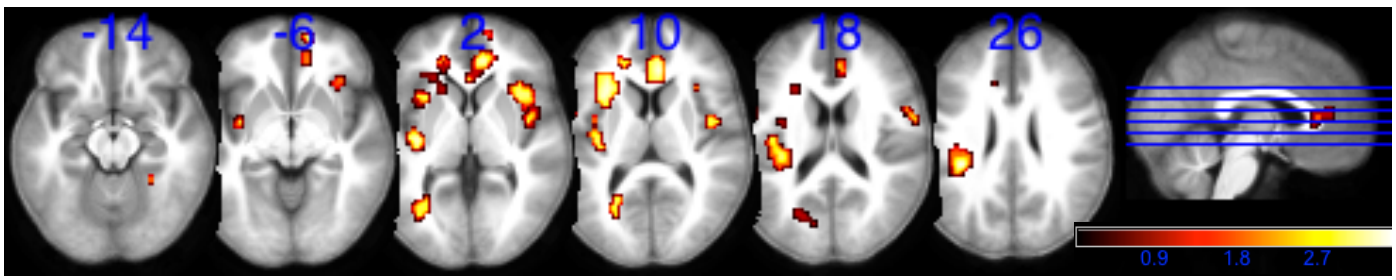


Figure 3.14 fMRI Interactions between Reward and Emotion in HC v ARMS participants outside the primary ROI network. Z coordinates ar displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p< 0.005.

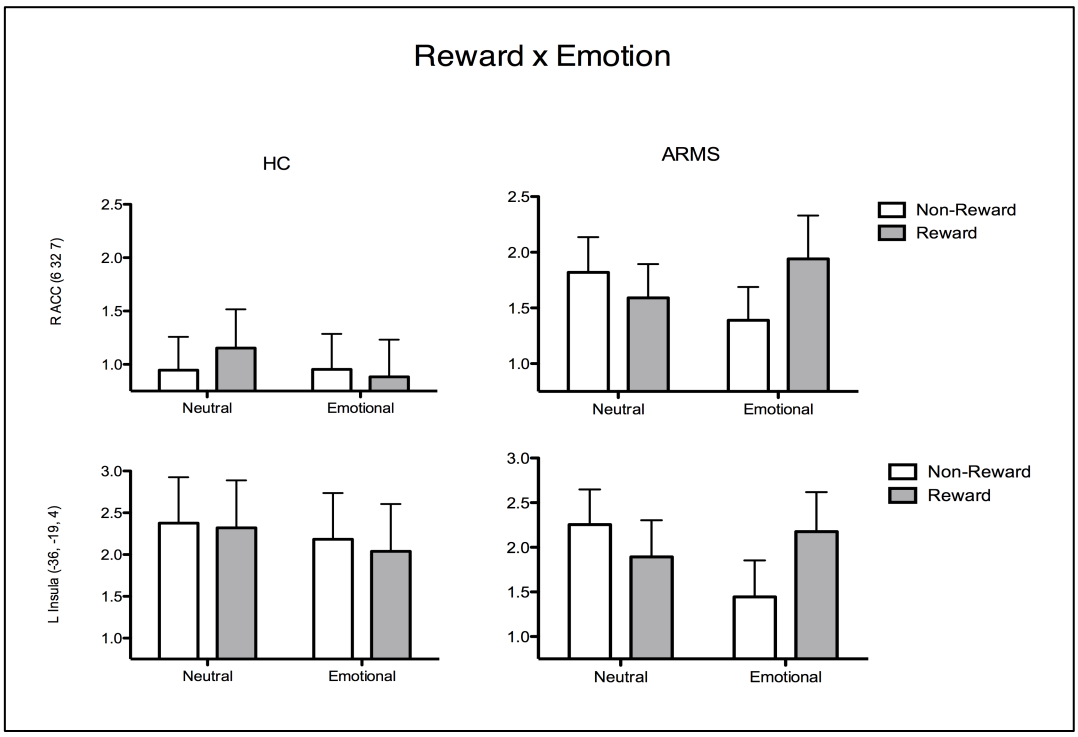


Figure 3.15 Reward x Emotion Interactions in R ACC (top) and L Insula (bottom) in HC (left) v ARMS (right). Columns show mean activation +/- SEM

3.4.5.5 Novelty x Emotion

There were no significant group differences in the interaction of novelty and emotion in the primary ROI network, but group differences were evident outside these regions in the right insula and right temporal pole (figure 3.17). Here the interactions were similar to those seen with reward and emotion; activations in the right insula in ARMS subjects were most pronounced for novelty in the context of emotion, but not for neutral scenes (figure 3.18).

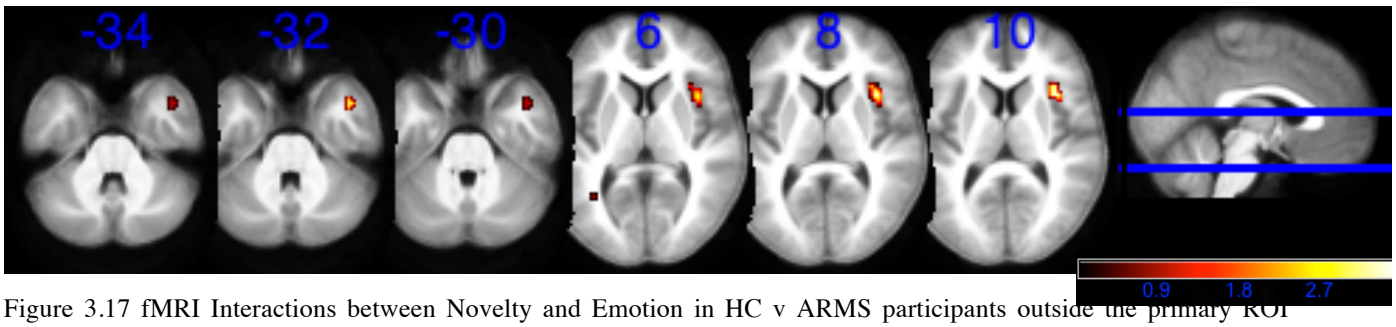


Figure 3.17 fMRI Interactions between Novelty and Emotion in HC v ARMS participants outside the primary ROI network. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p< 0.005.

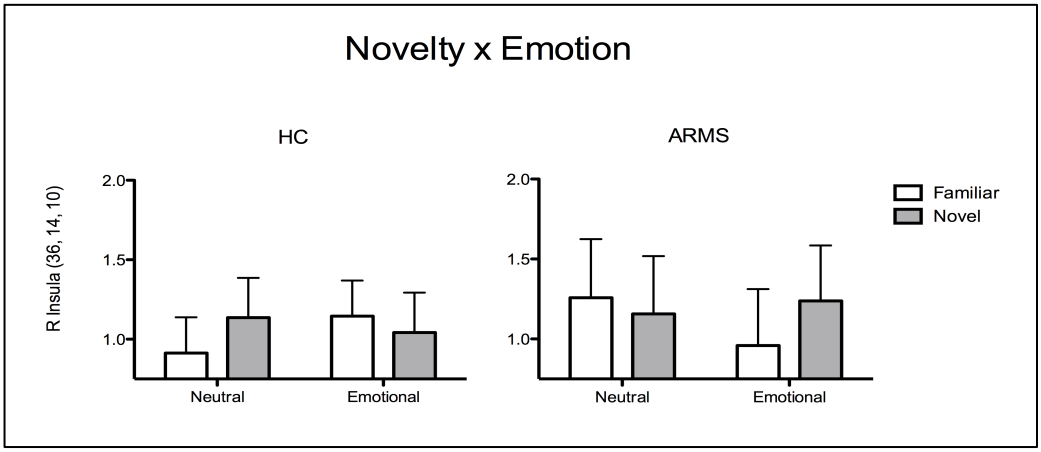


Figure 3.18 Novelty x Emotion interaction in right insula in HC (left) v ARMS (right). Columns show mean activation +/- SEM

3.4.5.6 Reward x Novelty

There was a group difference in the interaction between reward and novelty in the midbrain, at trend level. In ARMS subjects, reward activations were greater in novel scenes (table 3.5 figure 3.19 3.20).

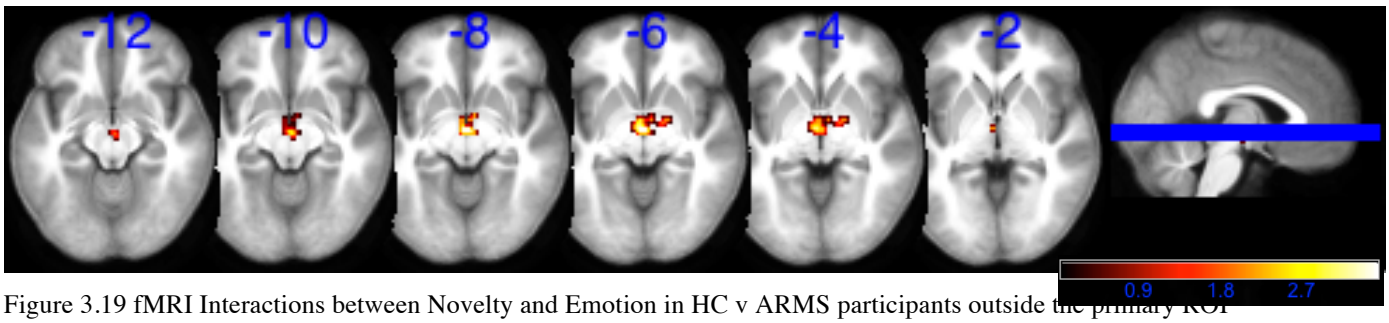


Figure 3.19 fMRI Interactions between Novelty and Emotion in HC v ARMS participants outside the primary ROI network. Z coordinates are displayed in blue. Images are thresholded for visualisation at whole brain uncorrected p< 0.005

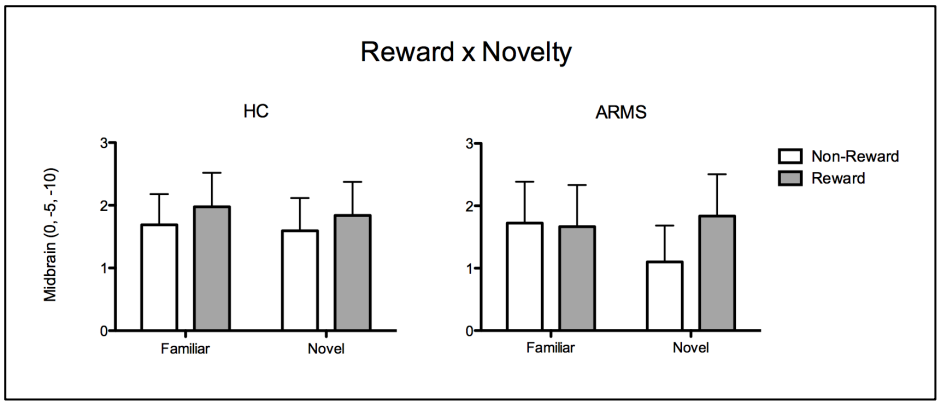


Figure 3.20 Reward x Novelty interaction in the midbrain in HC (left) v ARMS (right). Columns show mean activation +/- SEM

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3.5 Discussion

3.5.1 Summary of the main findings

In this chapter I compared healthy participants and those with an At Risk Mental State for psychosis using fMRI with the Salience Integration Task (SIT), probing the relative influence and interactions of three salient aspects of otherwise similar visual scenes: reward anticipation, novelty and negatively valenced emotion. ARMS participants demonstrated differences from controls in delayed recognition and augmented activation to reward anticipation in bilateral regions of the ventral striatum/pallidum, There was also preliminary indicators of group differences in the interaction of emotion with reward in the left ventral striatum; in ARMS participants relative to controls this region was hypersensitive to negative emotional stimuli in an reward-relevant context. A difference in the reward-emotion interaction was also evident in the ACC and bilateral insulae, areas that have previously been implicated in salience processing in controls (Seeley et al., 2007; Sridharan, Levitin, & Menon, 2008). A trend to a similar group difference was seen in the interactions of reward and novelty in the midbrain. Collectively, these results provide the first evidence that alterations in the processing of reward and emotional salience, at both the behavioural and the neural level, are evident prior to the onset of frank psychosis.

3.5.2 Overactivation to reward anticipation in ARMS participants: 'hyper'-salience rather than 'dys'-salience?

While previous studies in psychosis have focused on reward related salience, my work sought to also investigate the roles of novelty and emotion. The design of my paradigm also allowed me to examine interactions between these different aspects of salience. The data from the

work using the SIT task in controls (chapter 2) indicated the particular importance of emotion in these interactions in normal salience processing.

Previous work has demonstrated abnormalities in reward anticipation and reward prediction error in both medicated and medication -free participants with psychosis (Juckel et al., 2006; Murray et al., 2008). In these studies, the main finding has been of reduced striatal activation in patients for the salient - neutral contrast (see table 1.1 chapter 1). As these are contrasts between two conditions, a net reduction in activation can be interpreted either in terms of increased activation in patients to the neutral stimulus (taken as evidence of aberrant salience), and/or of reduced activation in patients to the salient stimulus (taken as evidence of reduction in salience). These findings have been largely supported by within-patient group correlations between these reductions in activation with negative symptoms (Juckel et al., 2006), and also recently with positive symptom scores (Nielsen et al., 2012).

To date there have been no published studies of salience processing in clinical or genetic high risk psychosis samples, and the extent to which salience abnormalities precede the onset of psychosis is thus unclear. The model of aberrant salience in psychosis emphasizes the phase-specificity of the relationship between altered salience processing, dopamine dysfunction, and the formation of psychotic symptoms (Kapur, 2003). In the current study, application of the SIT paradigm in ARMS subjects revealed hyperactivation to reward anticipation, with the maximal group difference in the ventral pallidum, a major projection target of the accumbens in the outflow path from the striatum (Lisman & Grace, 2005). This raises the possibility of a 'hypersalient' period prior to the onset of frank psychosis (Kapur, 2003). This resonates with phenomenological accounts of the prodromal period, which describe heightened vividness and *increased* salience and meaning from sensory stimuli that would usually be detected as salient, just less so.

"…my senses were sharpened, sounds were more intense and I could see with greater clarity, everything seemed very clear to me. Even my sense of taste seemed more acute…."(Bowers & Freedman, 1966)

Altered activation during salience processing in the ARMS is consistent with evidence from PET studies that striatal presynaptic dopamine availability is increased in this group (Howes et al., 2009). In fMRI studies, the signal related to reward anticipation is likely to be at least partly related to dopamine signaling (da Silva Alves et al., 2011; Knutson & Gibbs, 2007; Schott et al., 2008), so it is not surprising that reward processing may be abnormal in ARMS participants. Presynaptic dopamine levels, which probably relate more to 'tonic' than 'phasic' dopamine neuron firing, may increase the gain of phasic dopamine release, for example, as during reward anticipation. A moderate elevation in presynaptic dopamine levels in the ARMS could first increase normal salience. With high elevations salience processing could become uncoupled from salient stimuli, leading to the experience of aberrant or 'dys'salience. This is consistent with descriptions of the experience of intoxication with illicit dopaminergic drugs such as amphetamine, leading to energisation, hypervigilance and a vivid sensorium, and taken in larger and more sustained doses, psychosis (http://www.merckmanuals.com).

People with an ARMS may be experiencing something analogous to what Grace and colleagues describe as an 'activating context', whereby behaviourally salient stimuli elicit increased activation in salience processing networks, and moderately increased striatal dopamine output (figure 3.20B).

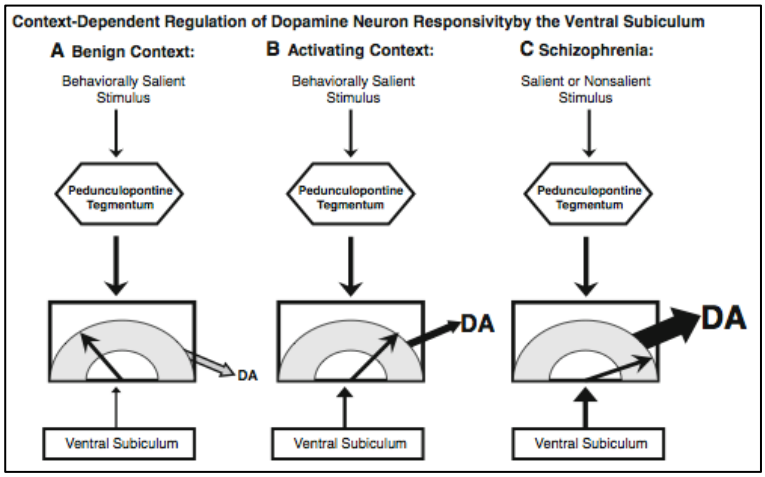

Figure 3.20 Participants experiencing attenuated psychotic symptoms at high clinical risk for psychosis may be as if in a constantly 'activating context', whereby behaviourally salient stimuli lead to greater activation.

At this stage activation contrasts between salient and non-salient stimuli are increased. In psychosis, both salient and non-salient stimuli lead to maximal activation (figure 3.20C), and the contrast between them is reduced – hence most studies in psychosis find reduced activation relative to controls (eg Juckel et al 2006, see table 1.1 chapter 1).

There are a number of important caveats to this interpretation. The majority of the ARMS participants will not make a transition to psychosis, and at this stage we are not able to distinguish those that will. There are other reasons why the results may have been different in ARMS and psychosis – including different tasks and methods of analysis. Many earlier studies included participants on medication with smaller group sizes. This is an advantage of the current sample, as even one dose of an antipsychotic significantly alters striatal function (Handley et al., 2012) and structure (Tost et al., 2010). The best way to address the issue is to do a longitudinal study, re-scanning participants on the same task after a follow up period.

The effects of stimulus novelty have not been previously examined in subjects with psychosis or an ARMS, despite novelty processing being influenced by dopamine function, and constituting a significant component of normal salience processing. In the present study, there were no significant differences between groups for the main effect of novelty at either the

behavioural or the neural level. This may be in part related to a relative lack of power for this particular contrast relative to the other. Similarly, there were no significant group differences for the main effect of emotion. In this case, the absence of group differences is not attributable to a lack of power for this contrast, as when studied in healthy controls, it was associated with the most significant effects (Chapter 2.6.2). Nevertheless, the lack of differences is surprising, given the prominence of emotional processing abnormalities in the ARMS, and the relatively high levels of anxiety and depression symptoms in this group (Aleman & Kahn, 2005; Seiferth et al., 2008).

3.5.3 ARMS participants show sensitivity of reward processing to emotion in the ventral striatum and 'salience network'

Although there were no main effects of emotional salience on activation, there was evidence that ARMS subjects may show increased sensitivity to aversive emotional stimuli when these are encountered in a motivationally relevant context. Emotion augmented reward related activation in the ventral striatum in ARMS subjects relative to controls, although this did not reach corrected significance. This resonates with suggestions from cognitive psychological research that the involvement of emotion in psychotic symptoms such as delusions and hallucinations distinguishes clinical psychosis with its attendant distress and functional impairment from psychotic like experiences in otherwise healthy individuals (Freeman & Garety, 2003).

A similar group difference in the interaction of emotion and reward was evident in the ACC and the insula bilaterally, areas that appear to form a network that facilitates salience-driven switching between default mode and central executive networks (Sridharan et al., 2008). Abnormalities in the structure, function and connectivity of these areas are evident in patients schizophrenia and in subjects with an ARMS (Broome et al., 2009; Crossley et al., 2009;

Mechelli et al., 2011; Palaniyappan, Mallikarjun, Joseph, White, & Liddle, 2011; White et al., 2010). The ACC is also involved in both reward processing and emotional regulation (Bush & Luu, 2000), while the anterior insula plays a prominent role in interoceptive awareness and has prominent limbic connections, particularly with the amygdala (Nagai & Kishi, 2007).

These results suggest that ARMS subjects may be sensitive to the effects of aversive emotion when these occur in a reward-relevant or incentivized context, and that this is related to functional alterations in brain regions implicated in the processing of reward, emotion and overall salience.

3.5.4 ARMS participants demonstrate differences in delayed recognition related to reward and emotion

The behavioural correlates of these fMRI differences were more difficult to interpret. There were no significant group differences in reaction time; suggesting that the group differences in activation were not attributable to differences in processing speed. Recognition hit rate differences were evident between groups to reward at 1hr (ARMS showing a reduced difference) and emotion at 24hr (ARMS showing a greater difference), perhaps reflecting differences in the way these stimuli were encoded or consolidated in ARMS participants. However there were also differences in false alarm rates, such that discrimination accuracies were largely similar between groups. It is not clear which of these measures of memory is the more relevant; increased salience of a particular stimulus may relate to increased recognition hit rate or discrimination accuracy but also to either increases or decreases in false alarms; for example ARMS subjects had reduced reward related difference in hit rate and discrimination accuracy but also a reduced false alarm elevation. There were also baseline group differences, further confounding any interpretation of differences; despite the group difference on reward for discrimination accuracy, the rate of accurate discrimination of reward cues was the same

in both groups. Novelty effects on later recognition are confounded by the effects of pre-familiaristion. Relating these in detail to the fMRI data is also complex, and may be mediated by a number of unmeasured factors; fMRI and recognition rate are proxies for the underlying neural and cognitive processes of interest. Taken together the behavioural data can provide only broad support for alterations in reward and emotional aspects of salience in the period prior to psychosis.

3.5.5 Limitations

As in the previous chapter, the factorial event related design of the SIT allowed examination of the main and interactional effects of reward, novelty and emotion, but did so at some cost to power when compared to single factor cognitive subtraction and block designs. For the interactional effects in the ventral striatum robust correction for multiple comparisons was not possible, and the interaction findings in this region should therefore be considered preliminary. Behavioural differences were not clearly interpretable in terms of the fMRI results although group differences were evident in each aspect of salience examined, whether in terms of recognition hit rate, false alarms rate or recognition accuracy.

3.5.6 Conclusions

These results suggest that the ARMS is associated with heightened salience, especially with respect to reward and emotional aspects of salience. These effects were particularly linked to altered activation in the ventral striatum/pallidum. The results are consistent with data from studies of reward salience in patients with psychosis, in that they implicate the striatum, but ARMS subjects showed greater, rather than reduced activation. This may reflect methodological differences between the studies in the two patient groups, particularly the

confounding effects of antipsychotic medication in previous studies. However, it is also possible that salience processing is altered in different ways at different stages of psychosis: this issue could be addressed in longitudinal studies. Further work could also examine the neurochemical basis of these effects.

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4. The role of presynaptic dopamine in salience processing in individuals at risk of psychosis

4.1 Background

Having considered 3 dimensions of salience processing from behavioural and neurofunctional points of view, first in health and then compared to the early stages of psychotic illness, we were interested in the neurochemical basis of altered salience processing. There is evidence that dopamine may be involved in salience processing whether conceived in terms of reward (Flagel et al., 2011; Schultz, Tobler, & Fiorillo, 2005; Wittmann et al., 2005), novelty (Bunzeck & Duzel, 2006; Redgrave & Gurney, 2006) or emotion (Jabbi et al., 2012; Kienast et al., 2008; Siessmeier et al., 2006), and that brain dopamine levels are abnormal from the early stages of psychosis (Howes et al., 2009) and influence its subsequent course (Howes et al., 2012; Howes, Bose, Turkheimer, Valli, Egerton, Stahl, et al., 2011b). We were therefore interested in testing whether dopamine levels might relate to altered salience processing, as measured by the Salience Integration Task. Subjects with psychosis show modestly elevated striatal dopamine levels relative to controls measured in terms of dopamine release (Laruelle & Abi-Dargham, 1996) and baseline D2 receptor binding (Laruelle et al., 1997), and large and significant elevations in presynaptic dopamine synthesis using the PET radiotracer ^{18}F-DOPA (reviewed in Howes et al., 2012). Studies of subjects with an At Risk Mental State show elevated baseline levels of presynaptic dopamine synthesis relative to controls (Howes et al., 2009), which is driven at baseline by those who go on to later transition to psychosis (Howes, Bose, Turkheimer, Valli, Egerton, Valmaggia, et al., 2011a) who also show a further increase with transition (Howes, Bose, Turkheimer, Valli, Egerton, Stahl, et al., 2011b).

Dopamine D2 receptor blockade is the hallmark of effective antipsychotic medication (Kapur & Mamo, 2003) however such treatment ,whilst effective at dampening positive psychotic symptoms does not cure, and leads to unwanted side effects related to dopamine blockade elsewhere, such as in the nigrostriatal pathway leading to parkinsonism and the tuberoinfundibular pathway leading to hyperprolactinemia (Kapur & Mamo, 2003). Several commentators have therefore suggested that the primary abnormality may lie several synapses 'upstream', via dysfunctional NMDA or GABA receptors on inhibitory interneurons to glutamatergic projections to midbrain dopamine cells(Grace, 2011; Olney, Newcomer, & Farber, 1999). One proposed site of such a primary abnormality is the hippocampus, and Grace and colleagues demonstrate in mice that hippocampal outputs drive midbrain dopamine output; blockade of the ventral subiculum of the hippocampus leads to a reduction in midbrain dopamine cell firing (Lisman & Grace, 2005).

Using a neurodevelopmental lesion model of schizophrenia in mice they then demonstrate that overactivity in the ventral subiculum drives increased midbrain dopamine cell activity (Lodge & Grace, 2008; 2009). In humans the hippocampus is a key site of abnormality in schizophrenia; structural and functional abnormalities are evident here from the earliest stages (Tamminga, Stan, & Wagner, 2010; Velakoulis et al., 2006; Wood, Kennedy, Phillips, & Seal, 2010) thought to result from the effects of neurodevelopmental insults and early stress and mediated by cortisol and glutamate excitotoxicity. However a decrease in function and structure does not necessarily imply a decrease in activity, and there is increasing evidence that there is increased activity in hippocampal subfields at rest in schizophrenia, that correlates with psychotic symptoms (Schobel et al., 2009).

Dopamine cells exist into two distinct states, exhibiting burst or phasic firing only when in a tonically active state (Grace & Bunney, 1984). Hippocampal input is thought to regulate tone - the number of dopamine cells which are available to fire in a phasic manner when stimulated

- thus regulating the 'gain' of the system according to context (Floresco, West, Ash, Moore, & Grace, 2003; Lodge & Grace, 2006). It is not yet clear how these tonic and phasic states of activity relate to measures from neurochemical imaging. However, measures of presynaptic dopamine synthesis such as ^{18}F-Dopa uptake, which reflect the overall availability of dopamine for release into the synapse may relate best to tonic control of dopamine firing, while measures of dopamine release, such as displacement of ^{11}C-Raclopride binding may relate to burst firing. If so, according to the Grace model, ^{18}F-Dopa measures should reflect the extent to which dopamine tone is being subject to hippocampal drive. This may be most evident in in the striatum where dopamine axons terminate onto post-synaptic receptors. ^{18}F-Dopa measures from the Substantia Nigra/VTA, the site of the dopamine cell bodies, would reflect release onto auto-receptors (Grace, Floresco, Goto, & Lodge, 2007).

In my previous work on salience processing in healthy participants, there was hippocampal activation to novelty, emotion and in the interaction of both of these with reward. The first aim of the work in the present chapter was to examine the relationship between these hippocampal responses and measures of dopamine synthesis in the striatum.

The second objective was to investigate whether these relationships would be altered in people with an ARMS. In my earlier fMRI study (Chapter 3), ARMS subjects showed greater ventral striatal activation than controls when processing reward. In addition, reward augmented striatal responses to emotion in ARMS participants but not in controls.

I hypothesized that dopamine output from the midbrain, as indexed by presynaptic synthesis capacity measured by ^{18}F-DOPA influx rate (Ki) in the striatum, would relate to hippocampal BOLD related activation by salient reward, emotion and novelty related visual stimuli, and that for reward and emotion this relationship would be significantly altered in ARMS subjects relative to controls.

However, because the putative relationship between hippocampal activation and striatal dopamine output may be mediated through the midbrain, I also assessed the relationship between activation to salient stimuli in the midbrain and striatal dopamine output. I hypothesized that presynaptic striatal dopamine synthesis capacity measured by 18-FDOPA Ki would relate to midbrain activation to reward, novelty and emotion related visual stimuli, and that for reward and emotion this relationship would be altered in those at risk for psychosis.

4.2 Methods

4.2.1 FDOPA methods

The PET acquisition protocol and parameters were as described in Howes et al (2009). Briefly, PET data acquisition was performed using an imaging system (ECAT/EXACT3D; Siemens/CTI, Knoxville, Tennessee) that has a mean (SD) spatial resolution of 4.8 (0.2) mm and a sensitivity of 69 cps/Bq/mL. High-resolution images of the whole brain were reconstructed from 95 planes with a section spacing of 2.425 mm. Subjects received carbidopa (150 mg) and entacapone (400 mg) orally 1 hour before imaging (Sawle, Burn, Morrish, & Lammertsma, 1994) to reduce the formation of radiolabeled ^{18}F-DOPA metabolites (Cumming, Léger, & Kuwabara, 1993). Data were acquired on an ECAT HR+ 962 PET scanner (CTI/Seimens) in 3D mode, with an axial field of view of 15.5cm. Head position was marked and monitored via laser crosshairs and a camera and minimized using a light head-strap. A 10-minute transmission scan was performed prior to radiotracer injection to correct for attenuation and scatter.

Approximately 180 MBq of ^{18}F-DOPA was administered by bolus intravenous injection 30

seconds after the start of the PET imaging. Emission data were acquired in list mode for 95 minutes, rebinned into 26 time-frames (comprising a 30-second background frame, four 60-second frames, three 120-second frames, three 180-second frames, and fifteen 300-second frames.

To correct for head movement during the scan, nonattenuation corrected dynamic images were denoised using a level 2, order 64 Battle-Lemarie wavelet filter (Turkheimer, Aston, Asselin, & Hinz, 2006) and individual frames were realigned to a single frame acquired 5 minutes after ^{18}F-DOPA injection using a mutual information algorithm (Studholme, Hill, & Hawkes, 1996). The transformation parameters were then applied to the corresponding attenuation-corrected frames, and the realigned frames were combined to create a movement-corrected dynamic image (from 6 to 95 minutes following ^{18}F-DOPA administration) for analysis.

In Montreal Neurologic Institute (MNI) space, standardized volumes of interest (VOI) were defined bilaterally in the limbic (ventral), associative (precommisural dorsal caudate, precommisural dorsal putamen and postcommisural caudate), and sensorimotor (postcommisural putamen) subdivisions of the whole striatal VOI as previously described (Martinez et al., 2003). The cerebellar reference region was defined using a probabilistic atlas (Hammers et al., 2003). An ^{18}F-DOPA template was normalized together with the VOI map to each individual PET summation image using the statistical parametric mapping suite SPM5 (http://fil.ion.ucl.ac.uk/spm). This procedure allowed VOIs to be placed automatically on individual ^{18}F-DOPA PET images without observer bias. As I was interested in dopamine output relevant to cognitive and emotional processing rather than motor function I focused on Ki values from the whole striatum and its limbic and associative subdivisions.

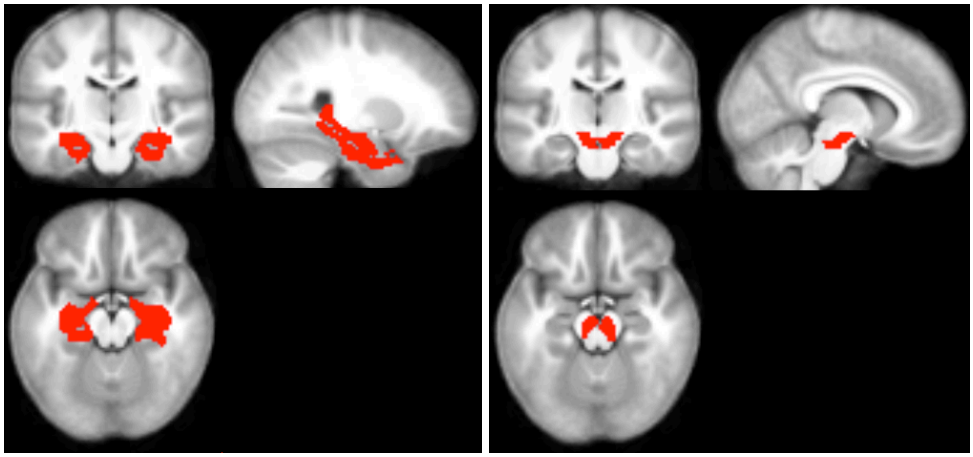
^{18}F-DOPA utilization, relative to the cerebellar reference tissue (Ki), was calculated for each

^{18}F-DOPA utilization, relative to the cerebellar reference tissue (Ki), was calculated for each VOI both uni- and bilaterally using graphical analysis, adapted for a reference tissue input function (Hartvig et al., 1991; Hoshi et al., 1993; Patlak & Blasberg, 1985).

4.2.2 Integration of PET and fMRI data

FDOPA Ki values were entered in as covariates of interest into the fMRI analysis in SPM8 at the 2nd (group) level. Left and right values were combined. A 1-sample t-test at the 2nd level was performed for the within group contrast, and a 2-sample t-test for between group comparisons. In the first analysis I was primarily interested in the relationship between Hippocampal activation to salient visual cues and dopamine output, and restricted the SPM analysis to this region. I formed a mask consisting of bilateral Hippocampal and parahippocampal regions from the Automated Anatomical Labeling Atlas (Tzourio-Mazoyer et al., 2002). I thresholded significant results at Family Wise Error corrected p=0.05 for multiple comparisons, minimum contiguous voxels per cluster =3.

For the second analysis of midbrain activation relating to striatal fDOPA Ki I used a midbrain mask drawn on the average T1 image of the subjects used in the study covering the region of the combined Substantia Nigra (SN) and the Ventral Tegmental Area (VTA figure 4.1B).



A. AAL Hippocampus/PHG B. SN/VTA

Figure 4.1 ROI Masks used in analysis superimposed on the averaged T1 of all subjects

I conducted a final exploratory whole brain analysis using the same method, thresholded at p=0.005 uncorrected, reported in supplementary results. For illustrative purposes all figures display fMRI activations thresholded at p<0.005 uncorrected. Scatter plots show mean ROI 18-FDOPA Ki values against SPM parameter estimates taken from the peak voxel of the specified contrast.

4.2.3 Participants

Approximately half of the participants who underwent fMRI scanning also participated in the PET scanning session. Sixteen participants with an At Risk Mental State for Psychosis (mean(SD) age=21.9 (5.0), 7 males, 9 BME, 15 right handed) and 16 healthy controls (mean (SD) age=24.9(3.4), 7 males, 7 BME, 13 right handed) provided written consent to undergo PET scanning. The study was approved by the Hammersmith Research Ethics Committee. PET scanning was not completed in one ARMS participant due to failure to meet radiotracer quality control standards, and the data from 1 further ARMS participant and 2 healthy controls was not included as the time between carbidopa /entacapone dosing and scanning was less than 1 hour, leading to possible uptake of FDOPA outside the brain. Data from 14 ARMS and 14 control participants was included in the final analysis.

4.3 Results

4.3.1 ^{18}F-Dopa in ARMS vs healthy controls

There were no significant differences in ^{18}F-DOPA Ki between participants with an ARMS and matched controls, either in the whole striatum or its subdivisions, or in the midbrain.

These subjects formed part of a larger sample that showed elevated presynaptic dopamine

levels relative to controls in the associative striatum (Egerton et al 2012).

4.4 ^{18}F-Dopa PET and Reward Salience processing

4.4.1 Reward Salience and Striatal ^{18}-F-DOPA in Healthy Controls

There were no significant relationships between Reward predicting cue related hippocampal activation and FDOPA Ki in the whole striatum, or in its limbic or associative subdivisions. Similarly there were no significant relationships between midbrain activation and Ki in these areas. In the exploratory whole brain analysis there were no other areas of relationship between FDOPA Ki in the striatum and activation to reward.

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HC ROI analyses			Size	peak						
fMRI contrast	PET ROI striatum	+/-	k	t	z	p(unc)	p(FWE WB)	p(FWE ROI)	MNI x,y,z {mm}	Location
Reward	Whole	+/-	NIL							
	Limbic	+/-	NIL							
	Associative	+/-	NIL							
Novelty	Whole	pos	NIL							
		neg	NIL							
	Limbic	pos	17	5.07	3.64	<0.001	0.826	0.075	-24 -22 -11	L Hippocampus (subic)
			5	3.41	2.79	0.003	0.995	0.475	27 -25 -23	R PHG
			4	3.39	2.78	0.003	0.995	0.484	21 -7 -29	R Hippocampus (EC/subic)
		neg	NIL							
	Associative	pos	NIL							
		neg	NIL							
Emotion	Whole	pos	NIL							
		neg	243	6.8	4.28	<0.001	0.219	0.009	-24 -40 -11	L Hippocampus (subic)
				6.76	4.26	<0.001	0.227	0.009	-30 -25 -20	L Hippocampus (subic)/PHG
				5.45	3.79	<0.001	0.643	0.008	6 -22 -20	R Midbrain
	Limbic	pos	NIL							
		neg	NIL							
	Associative	pos	NIL							
		neg	240	5.4	3.78	<0.001	0.648	0.045	-30 -25 -20	L Hippocampus (subic)/PHG
			16	3.74	2.99	0.001	0.999	0.055	-12 -13 -11	L Midbrain

Table 4.1 Interactions between hippocampal/midbrain fMRI activation to Reward, Novelty and Emotional salience and Striatal ^{18}F-DOPA Ki values in healthy controls

ARMSvHC ROI analyses		size	peak						
fMRI contrast	PET ROI striatum	k	t	z	p(unc)	p(FWE WB)	p(FWE ROI)	MNI x,y,z {mm}	Location
Reward	Whole	NIL							
	Limbic	35	5.09	4.15	<0.001	0.081	0.019	-15 -22 -23	L Hippocampus (subic)
	Associative	NIL							
Novelty	Whole	23	3.83	3.35	<0.001	0.819	0.119	-15 -25 -20	L Hippocampus (subic)
	Limbic	5	3.16	2.86	0.002	0.988	0.384	-18 -28 -26	L PHG
	Associative	19	3.54	3.15	0.001	0.924	0.181	-15 -25 -20	L Hippocampus (subic)
Emotion	Whole	61	4.46	3.77	<0.001	0.411	0.005	6 -25 -20	R Midbrain (SN/VTA)
			4.08	3.52	<0.001	0.665	0.015	-3 -25 -26	L Midbrain (SN/VTA)
		50	4.01	3.47	<0.001	0.711	0.092	-27 -28 -23	L Hippocampus (subic)/PHG
	Limbic	NIL							
	Associative	9	3.41	3.05	0.001	0.97	0.296	-27 -28 -23	L Hippocampus (subic)/PHG
		4	3.26	2.94	0.002	0.988	0.059	9 -28 -20	R Midbrain (SN/VTA)
		5	3.2	2.89	0.002	0.992	0.067	-3 -28 -23	L Midbrain (SN/VTA)

Table 4.2 Interactions between hippocampal/midbrain fMRI activation to Reward, Novelty and Emotional salience and Striatal 18-FDOPA Ki values between ARMS participants and healthy controls

4.4.2 Reward Salience and Striatal ^{18}F-DOPA in ARMS vs controls

There was a significant difference between participants with an ARMS and healthy controls in the relationship between reward cue related activation in the left hippocampal subiculum (15, -22, -23) and ^{18}FDOPA Ki in the limbic striatum (p_{FWE}= 0.019, figure 4.2, table 4.2): in ARMS participants, greater hippocampal activation was directly related to greater 18-FDOPA Ki in the limbic striatum. This relationship was not evident in controls.

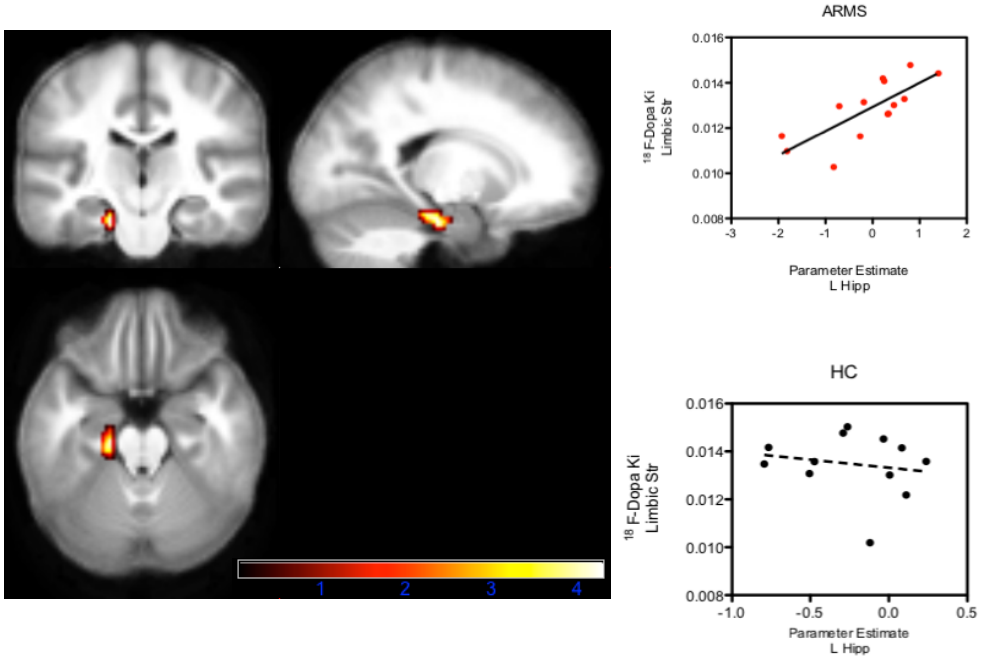

Figure 4.2 Difference between ARMS and controls in the relationship between left Hippocampal subiculum activation to reward cues and limbic striatal 18-FDOPA Ki.

This difference was specific to dopamine function in the limbic subdivision of the striatum. (table 4.2), and to hippocampal activation. There was no relationship with dopamine function in the whole striatum or its associative division, or with activation in the midbrain or any other area examined in the exploratory whole brain analysis.

4.5 ^{18}F-DOPA PET and Novelty Salience processing

4.5.1 Novelty Salience and Striatal ^{18}F-DOPA in Healthy controls

In controls, there was a trend for increased activation in the left hippocampus subiculum (-24, -22, -11) to cue novelty to be correlated with increased ^{18}F-DOPA Ki in the limbic subdivision of the striatum (p_{FWE}= 0.075, figure 4.4 table 4.1).

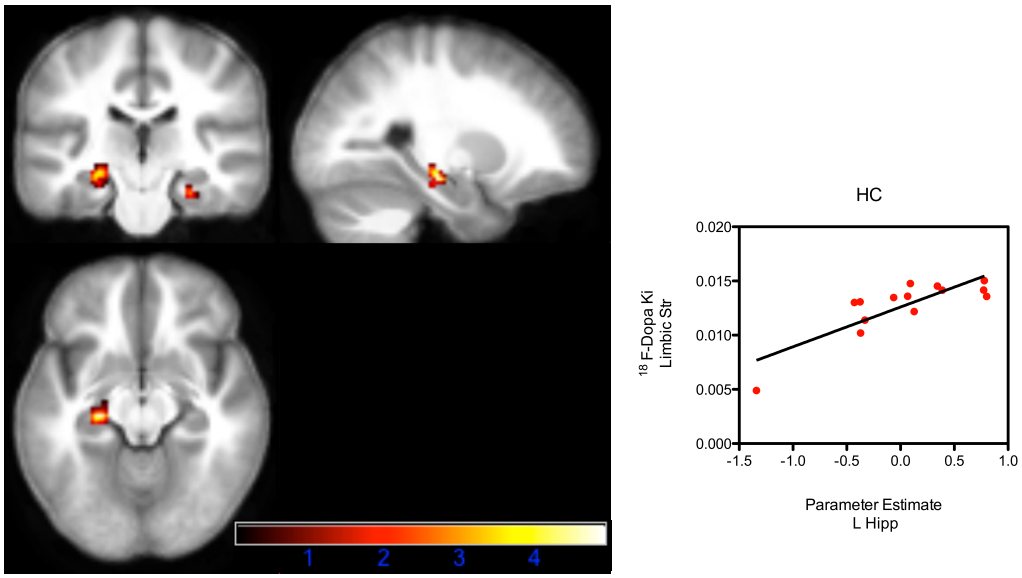

Figure 4.4 Trend towards increased activation in bilateral anterior hippocampus to novelty correlating with increased FDOPA Ki in the Limbic striatum in controls

This was specific to hippocampal activation and to the limbic striatum; there was no significant relationship between hippocampal activation with whole or associative striatal ^{18}F-DOPA Ki, or between midbrain activation and limbic striatal Ki.

In the exploratory whole brain analysis, increased activation in the left putamen and reduced activation in the left insula related to increased ^{18}FDOPA Ki measured in the associative striatum (Supplementary table 1).

4.5.1 Novelty Salience and Striatal ^{18}F-DOPA in ARMS vs Healthy controls

There was a trend for a group difference in the relationship between novelty associated hippocampal activation and ^{18}FDOPA Ki values in the whole striatum, and in the associative striatal subdivision (Figure 4.4, table 4.1). Novelty associated hippocampal activation was correlated with limbic striatal ^{18}FDOPA Ki in controls, but with associative striatal ^{18}FDOPA Ki in ARMS participants. There was no such difference for novelty associated activation in the midbrain, and no significant other areas of difference in the whole brain analysis.

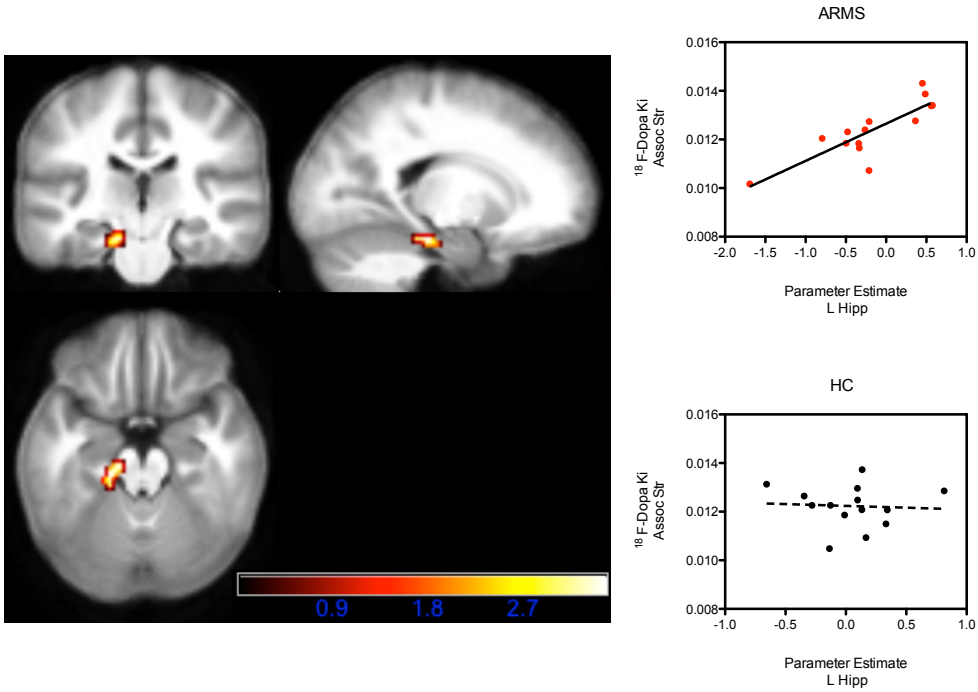

Figure 4.4 Non significant difference in relationship of L Hippocampal activation to novelty with FDOPA Ki in the associative striatum

4.6 18F-Dopa PET and Emotional Salience processing

4.6.1 Emotional Salience and Striatal ^{18}F-DOPA in Healthy controls

Activation elicited by negatively valenced emotional cues in the hippocampus correlated negatively with ^{18}FDOPA Ki in both the whole striatum and its associative subdivision (figure 4.5, Table 4.1). A similar relationship was evident between activation in the midbrain and the whole striatal and associative striatal Ki (p_{FWE}= 0.028, figure 4.5 table 4.1).

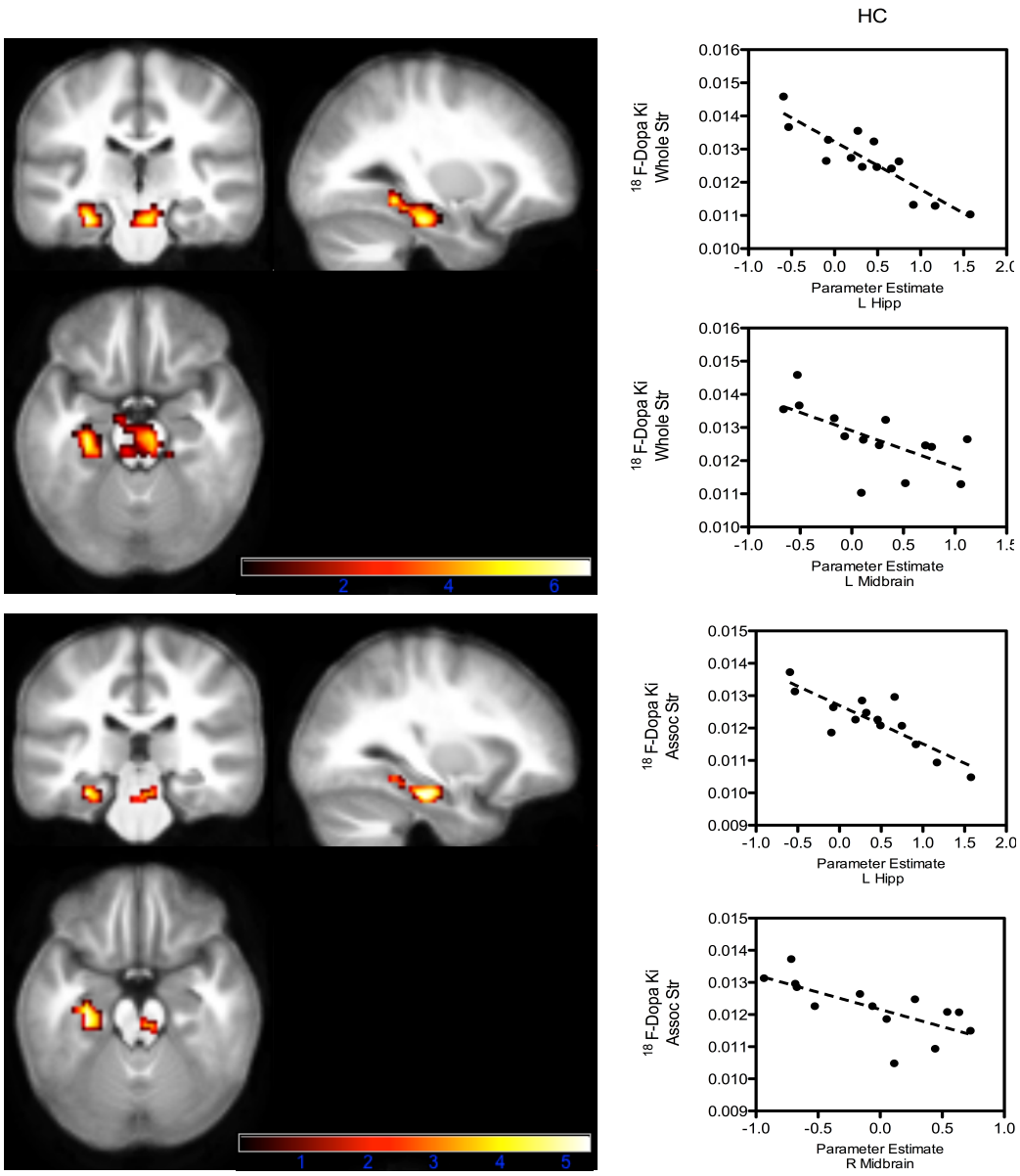

Figure 4.5 Hippocampal and midbrain activation to emotion in controls correlates negatively with pre-synaptic dopamine synthesis capacity in the whole striatum (top) and its associative subdivision (bottom)

In the whole brain analysis increased activation to emotional cues in a cluster in the right Dorsolateral Prefrontal Cortex was also related to increased ^{18}FDOPA Ki measured in the whole striatum and both limbic and associative subdivisions (table 4.2).

4.6.2 Emotional Salience and Striatal ^{18}F-DOPA in ARMS vs Healthy controls

There was a trend towards a difference between ARMS and control participants in the relationship between Emotion related left hippocampal activation and ^{18}FDOPA Ki in the whole striatum ($p_{FWE} = 0.092$, figure 4.6, 4.7 table 4.2). While in healthy controls there was a strong relationship between increased hippocampal activation to aversive emotional cues and reduced striatal presynaptic dopamine availability, this relationship was absent in ARMS. This difference was also evident with ^{18}FDOPA Ki measured in the associative striatum, but not the limbic striatum (table 4.2).

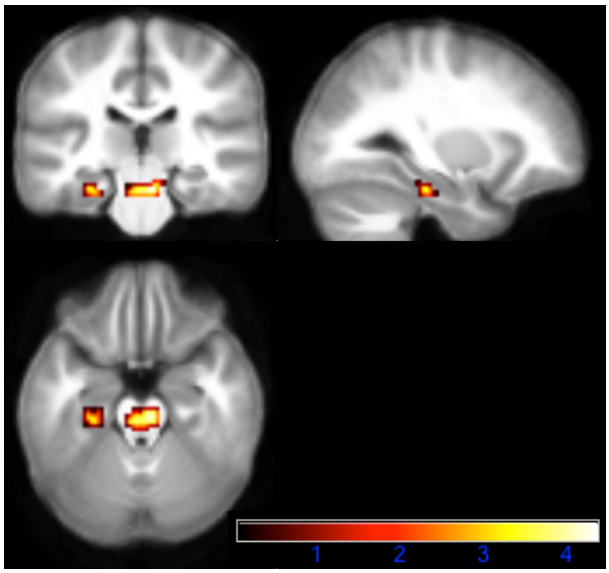

Figure 4.6 Group difference in relationship between pre-synaptic dopamine synthesis capacity in the whole striatum and hippocampal and midbrain activation to emotion.

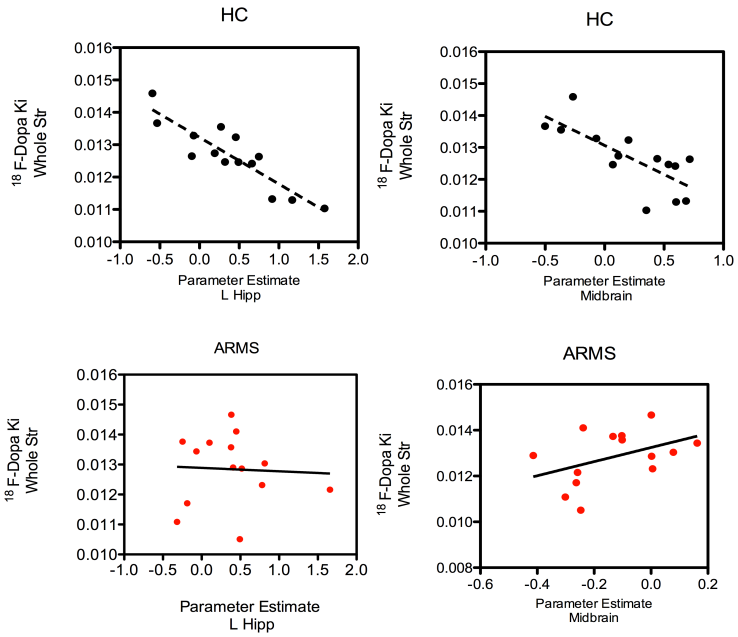

Figure 4.7 Hippocampal (left) and midbrain (right) activation to emotion in controls (top) correlates negatively with pre-synaptic dopamine synthesis capacity in the whole striatum but not in ARMS participants (bottom).

There was also a significant between group difference in the relationship of emotional cue elicited activation in the midbrain and ^{18}FDOPA Ki measured in the whole striatum (p_{FWE} =0.005 figure 4.6, 4.7, table 4.2); in controls, but not in ARMS, increasing midbrain activation to emotional cues was related to decreased ^{18}FDOPA Ki in the whole striatum. This difference was also evident as a trend with FDOPA Ki in both the associative and the limbic striatal subdivisions (table 4.2).

In the exploratory whole brain analysis there were also different relationships between ARMS and controls with limbic striatal ^{18}FDOPA Ki and activation in bilateral ACC, insulae, precuneus and occipital regions (figure 4.8). In these regions, increasing activation to emotional cues correlated positively with limbic striatal ^{18}FDOPA Ki in the ARMS group, but not in controls.

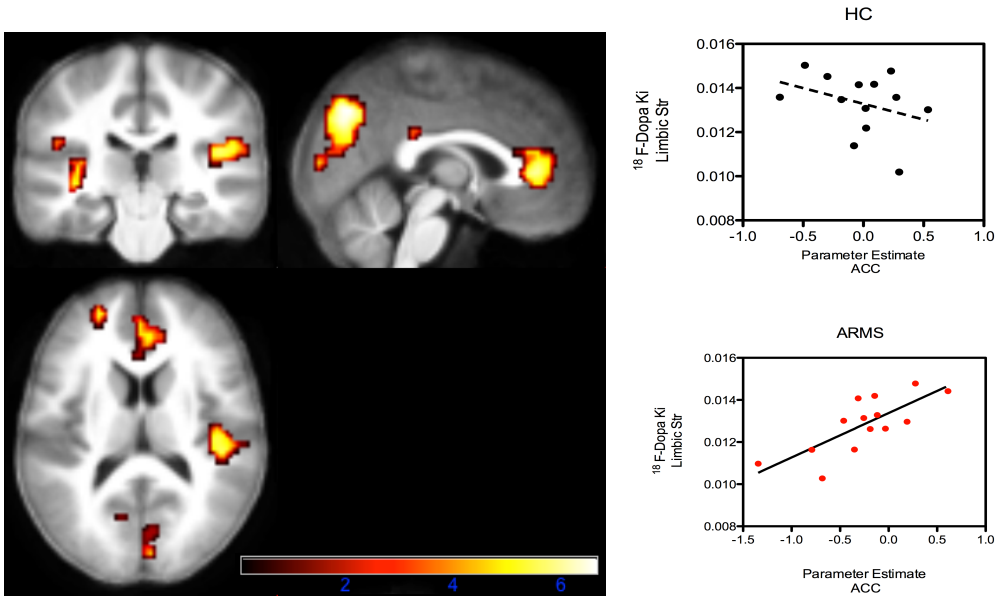

Figure 4.8 whole brain analysis of group differences in relationship between activation to Emotion and Limbic striatal ^{8}F-DOPA Ki. Scatter plots refer to ACC cluster.

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4.7 Discussion

In this study I combined ^{18}-FDOPA PET imaging with fMRI to explore the relationship between hippocampal and midbrain activation to salient visual stimuli and presynaptic dopamine synthesis capacity in the striatum of participants with an ARMS and controls. Following the predictions of the MAM animal model of schizophrenia (Lodge & Grace, 2009), I first tested the hypothesis that in healthy controls, hippocampal activation by salient stimuli would be directly related to dopamine function in the striatum. I then tested the hypothesis that this relationship would be altered in participants with an ARMS. I expected that reward and emotion would be the aspects of salience most associated with group differences in the relationship with dopamine function, as the most significant group differences in activation were seen with reward and emotion salience. 18-FDOPA PET scanning was used to measure pre-synaptic dopamine function, as this aspect of dopamine transmission is thought to index 'tonic' dopamine activity, which is the type influenced by descending outputs from the hippocampus (Lisman & Grace, 2005).

The first hypothesis was partially supported; in control participants, there were trends for activation to both emotion and novelty salience in the hippocampus to be related to dopamine synthesis capacity in the striatum. However, there was no relationship between hippocampal reward salience activation and striatal dopamine function.

My second hypothesis was more clearly supported; the relationship between hippocampal activation by salient stimuli and striatal dopamine function was altered in ARMS subjects, particularly in the reward and emotional dimensions, as anticipated. ARMS subjects showed a positive relationship between the level of striatal dopamine synthesis and the level of hippocampal activation to reward, but this relationship was not evident in controls.

Conversely, there was a negative relationship between hippocampal activation to emotion and striatal dopamine function that was not evident in ARMS participants. Both ARMS and control subjects showed positive relationships between hippocampal activation to novelty salience and striatal dopamine function, but these were evident in relation to different striatal subdivisions.

In the wider, uncorrected, whole brain analysis ARMS participants also showed positive relationships between striatal ^{18}-DOPA Ki and emotion elicited fMRI activations in the ACC and insula bilaterally, regions that have been collectively termed the 'salience network' (Seeley et al., 2007). These relationships were not evident in controls.

In healthy controls, striatal dopamine function was related to hippocampal activation to some aspects of salience, but not others. There were trends for novel visual cues, regardless of reward relevance or emotional content, to elicit hippocampal activation in the anterior left subiculum that was correlated positively with limbic striatal ^{18}-FDOPA Ki. This is consistent with the model of Lisman and Grace (2005): novelty signals, generated in the hippocampal subiculum by comparing new perceptual inputs via hippocampal subfield CA1 with predictions from CA3 then go on via multiple synaptic connections to drive midbrain dopamine output to striatal, frontal and recurrent hippocampal targets, the latter reinforcing memory via dopamine mediated long term potentiation (Lisman & Grace, 2005). In ARMS participants we found a similar relationship, although this was strongest with dopamine function in the associative rather than the limbic subdivision, and was evident at an uncorrected level only.

In healthy controls hippocampal activation to emotional cues, again centered on the anterior left subiculum, regardless of novelty or reward relevance, was negatively correlated with Ki values in the whole striatum, and in its associative subdivision. This was also true for activation in the midbrain, centred on the right substantia nigra/VTA. These relationships

were highly significant, and are in line with a similar recent finding from another group of activation to emotional salience (in this case dynamic emotional facial expressions) relating negatively to midbrain dopamine function measured by ^{18}-FDOPA PET in control participants (Jabbi et al., 2012). Jabbi et al however combine positive and negative emotional valence, and find midbrain ^{18}-FDOPA relationships with activation in a network of regions including the hippocampus, but also in the amygdala, insula, medial-frontal/orbitofrontal and cingulate cortices. They do not however report striatal ^{18}-FDOPA Ki values, which may provide greater reliability and signal to noise ratios than midbrain measures (Egerton, Demjaha, McGuire, Mehta, & Howes, 2010), and may be more interpretable in terms of midbrain dopamine output from axon terminals to projection target regions rather than local feedback to autoreceptors. Siessmeier et al (2006) did examine striatal presynaptic dopamine synthesis and found a relationship between ventral striatal ^{18}-FDOPA Ki and activation to positive emotional stimuli in the left ACC and right insula, and with dorsal striatal ^{18}-FDOPA Ki and activation to both positive and negative emotional stimuli in the left DLPFC. Using only negatively valenced emotional stimuli we replicated the DLPFC finding with ^{18}-FDOPA Ki measured in the whole striatum and both limbic and striatal subdivisions, but found no relationship with activation in ACC or insulae to negative emotional stimuli, suggesting a specificity for positive affect in these regions in health, while the DLPFC may respond to emotion regardless of valence.

Dopamine also modulates emotional processing more widely - Kienast et al (2008) find that dopamine tone in the amygdala measured using ^{18}F-DOPA correlates positively to fMRI activations to fearful stimuli in the amygdala, and in the ACC. We did not measure amygdala ^{18}F-DOPA Ki and are unable to make direct comparisons with these data.

Relationships between dopamine neurotransmission and emotional processing have not to our knowledge been previously examined in subjects with at high clinical risk of psychosis. In my

sample of ARMS participants, who were experiencing attenuated psychotic symptoms, I found an alteration in the relationship between activation and striatal 18-FDOPA Ki, suggesting that dopamine mediated processing of negative emotional stimuli was significantly altered. Firstly, the strong relationship between hippocampal activation to negative emotional stimuli and 18-FDOPA Ki in the whole and associative striatum that was evident in controls was absent in ARMS participants. That this was more specific to the associative rather than the limbic striatum may reflect the importance of fronto-striatal connections in the healthy processing of emotional stimuli, and suggests that this crucial process may be disturbed in those with attenuated psychotic symptoms.

Emotion dysregulation is a core feature of psychotic illness and these findings suggest that dopamine dysregulation may play a role in this aspect of the illness. The accompaniment of particularly aversive or threatening emotional aspects to psychotic-like experiences may be central in their development and maintenance (Freeman & Garety, 2003). The work in the previous chapter indicated that the presence of negative emotion selectively augmented ventral striatal, ACC and insula responses to reward in ARMS participants (chapter 3). In the present chapter, in a whole brain analysis, and at uncorrected statistical threshold, negative emotion elicited activation in the ACC and insulae was related to limbic striatal Ki in ARMS participants, but not controls. This relates to the finding by Siessmeier et al discussed above (Siessmeier et al., 2006), who found that positive but not negative emotional stimuli elicited activations in the ACC and insula were related to limbic striatal Ki. In ARMS subjects this relationship was evident with negative emotional stimuli, but we were unable to test the effect of positive stimuli.

Limbic striatal dopamine is known to play a role in reward anticipation (Schott et al., 2008) and we found that in ARMS participants, negative emotional content further augmented elevated reward related responses in both the limbic striatum and in the ACC and insulae. In

those experiencing attenuated psychotic symptoms it may be that frontal-dorsal striatal moderation of responses to negative emotional stimuli is diminished, which therefore drive increased ventral striatal responses, to for example, reward.

Reward processing was the aspect of salience that most differentiated the ARMS and control groups in terms of activation during the salience integration task (chapter 3). ARMS participants showed greater activation than controls to reward predicting visual cues in ventral striatal regions bilaterally (chapter 3). The work in this chapter shows that in ARMS there is an abnormal relationship between reward related activation in the hippocampus and a direct measure of dopamine in the striatum, as predicted by the Grace MAM model (Grace, 2011). In ARMS, but not in control participants, hippocampal activation, centered on the left subiculum, correlated positively with ^{18}-FDOPA Ki in the limbic striatum. This was specific to activation in the subiculum and to 18-FDOPA Ki in the limbic striatal subdivision. This is consistent with the notion that alterations in reward-related salience processing mediate the link between altered dopamine transmission and psychotic symptoms, as proposed by the aberrant salience hypothesis (Kapur, 2003). It also adds support to the concept that abnormal hippocampal overdrive of an essentially intact dopamine system leads to striatal hyperdopaminergia, rather than abnormalities lying within the dopamine system itself (Grace, 2011).

Using a voxelwise approach I found that the hippocampal region demonstrating relationships with activations to reward, novel and emotional stimuli with striatal dopamine synthesis capacity was consistently centered on the left anterior subiculum. Peak voxel locations were determined using an automated probabilistic atlas (Tzourio-Mazoyer et al., 2002) and confirmed manually (Mai, Paxinos, & Voss, 2008). The anterior hippocampus is the more 'limbic' portion of this structure, with multiple connections with the amygdala and related structures, has a clear role in context dependent fear learning (Maren & Fanselow, 1995), and

may more broadly reflect the affective context of stimuli (Grace, 2011). The subiculum is the area of major hippocampal outflow, and the anterior part is the human equivalent of the ventral region in mice (due to the different shape of hippocampus in humans). This region is a major site of lesions in animal neurodevelopmental lesion models of psychosis (Jones, Watson, & Fone, 2011), and the site of NMDA infusions to stimulate and TTX injections to disrupt increases in midbrain dopamine tone by altering the population of active dopamine neurons in the midbrain (Lodge & Grace, 2006). The current study therefore provides tentative support for the predictions of the MAM model of schizophrenia, in particular that overdrive of midbrain dopamine output results leading to psychotic symptoms from increased output from the ventral subiculum. This model suggests that this results from dysfunctional interneuron function within the ventral subiculum, resulting from underactive alpha-5 GABA receptors.

An alternate site of dysfunction is glutamatergic NMDA receptors on hippocampal interneurons (Olney et al., 1999), a proposal given support by the demonstration of an altered relationship in ARMS participants between hippocampal glutamate levels measured by magnetic resonance spectroscopy and striatal dopamine ^{18}-FDOPA uptake (Stone et al., 2010). Exploring these alternative sites of potential interneuron dysfunction is important future work, and has the potential to lead to new treatment targets (Stone & Pilowsky, 2007).

Group differences in the relationship between medial temporal activation by a verbal memory task and striatal 18-FDOPA PET have previously been demonstrated in a group of ARMS participants (Allen et al., 2011). The present findings support and extend these to include aspects of reward and emotional processing, both potentially relevant within an aberrant salience model of psychosis.

Overall this work provides tentative human in vivo evidence to support the predictions of the MAM animal model in the early stages prior to the onset of psychosis. Further work should extend this into samples with established psychosis, and include neurochemical work to facilitate the discovery of new therapeutic targets.

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5. Conclusion

5.1 What is 'Salience processing', and how can we test it?

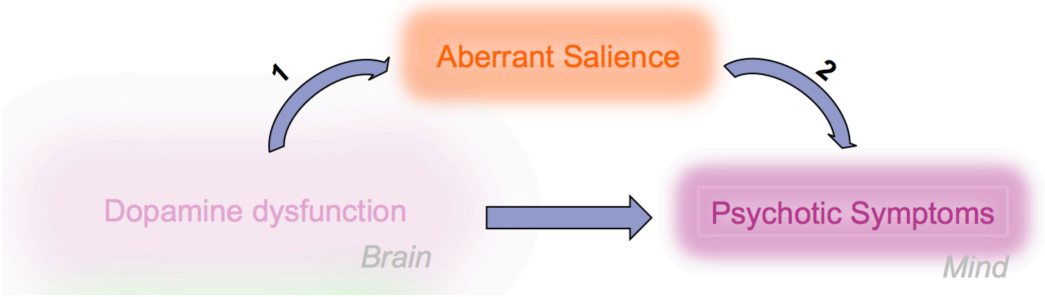

Figure 5.1 The Aberrant Salience Model of psychosis links brain and mind level explanations of psychosis

The aberrant salience model (Heinz, 2002; Kapur, 2003), simplified above, provides a link between the neurobiological and clinical aspects of psychosis (figure 5.1). It is influential amongst cognitive neuropsychiatric models of psychosis because it can provide a plausible account of symptom development and manifestations (especially delusions) and also because it can link these cognitive and psychological accounts to dopamine dysfunction (step 1 of model in figure 5.1). However, while salience has been a useful "heuristic" in bridging this gap – the original authors (Heinz, 2002; Kapur, 2003)) and subsequent users of this term have not operationalized it with any precision.

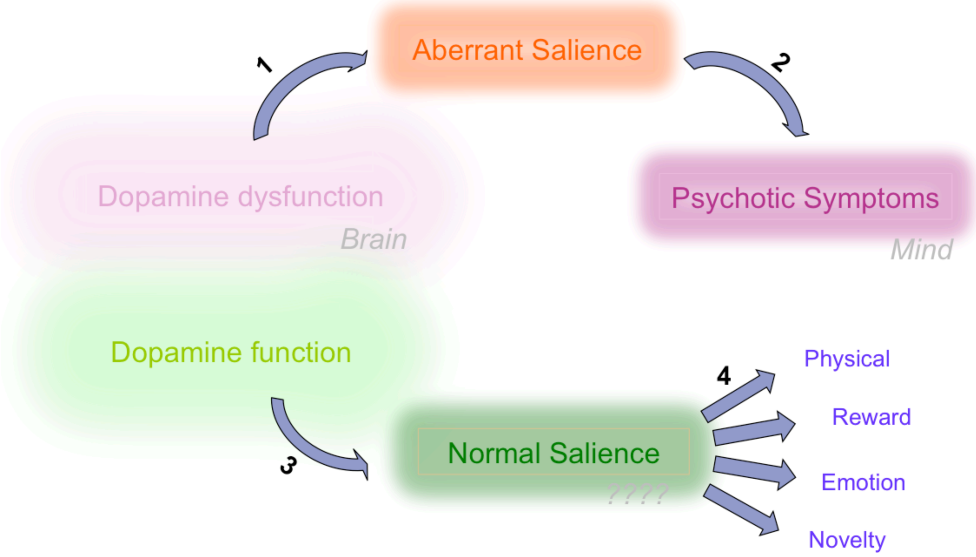

Figure 5.2 Expanded Aberrant salience model: function must be understood before dysfunction

This was the first question addressed in this thesis, and an important grounding for experimental testing of a model invoking aberrant salience (figure 5.2).

At the moment "salience" is a broad term commonly used in a number of fields. In trying to address this different authors have used different operationalizations of salience, for example reward prediction (Juckel et al., 2006), prediction error (Murray, Lappin, & Di Forti, 2008), explicit salience attributions for reward prediction (Roiser, Stephan, Ouden, Friston, & Joyce, 2010) or emotional content (Holt et al., 2006). It seems that each has picked up one element of salience as reflected in their paradigm rather than coming at it with a broader consideration of what constitutes salience overall in humans and therefore how best to capture its multidimensional nature, and how this may be altered in psychosis.

I consider by way of analogy the more developed and defined concept of salience in the field of vision research and robotics (chapter 1 p24), and note that it is integrative of a number of different visual features (colour, brightness, contrast, motion, spatial complexity) and representable as an overall 'map'. This map combines these features into a single salience

dimension, proportionate to brightness on the saliency map. More advanced are semantic-saliency maps being developed in robotics attempt to combine higher features with visual saliency to facilitate appropriate resource allocation and response selection (Meger, Forssén, Lai, & Helmer, 2008).

However there are as yet are no such 'higher feature' maps to satisfactorily model salience in humans. From the original concept as developed in the animal literature and as adapted in subsequent writings to the clinical situation (Heinz, 2002; Kapur, 2003) it seems that salient stimuli often 1) capture attention, thought and alter behaviour and 2) the ability of the stimuli to do so is mediated or moderated, in part, by dopamine.

Figure 5.3. Salient stimuli in humans are multifaceted

Rewarding, Novel and Emotional stimuli meet both sets of criteria – they are known to capture attention and alter behaviour and they are influenced by dopamine function. To the extent that these criteria accurately reflect the construct of salience then manipulations of

reward, novelty and emotion are likely to be manipulations of salience. Their interactions and relative contributions towards salience for particular individuals or groups is unknown, and a key question of this thesis.

However as discussed these criteria are far from complete or established, and as salience is necessarily subjective, it is difficult to access experimentally. In order to move this state of affairs forward I constructed a paradigm that allows comparison and interaction of these 3 stimulus dimensions on 3 simple measures, reaction time, recognition memory and neural activation in a pre-specified brain network that was derived from a relevant animal model. Within the context of the experiment these served as proxies of the behavioural, cognitive and neural aspects of salience processing. I considered that the greater the modulation of behaviour, cognition and neural activation by a specific dimension or interaction of dimensions, the more likely that stimulus was salient for the subject in question. Similar to previous attempts at capturing the phenomenon of salience, these criteria are necessarily another operationalization, with limitations.

For example if one uses the above criteria (changes in RT, memory and brain activation) it is very conceivable that subconscious priming may be able to alter these without the reward/novelty/emotion aspects of the stimulus being consciously accessible to the individual. There are numerous instances and reports of where these priming stimuli capture attention and change behaviour of the individual – though usually they do not actively engage conscious thought (Sheeran, Gollwitzer, & Bargh, 2013). While we concede that unconscious stimuli can also, under certain circumstances, achieve similar effects to consciously salient stimuli, that was not the focus of our experiments. In the current experiment attention and conscious visual processing of each stimulus was ensured by requiring a button press to all scenes aside from 2 NoGo control scenes, similar to the other scenes apart from detailed scene content. Errors in this aspect of task performance were less than 10%.

The more interesting question this raises is whether alterations in implicit priming, rather than explicit reward, novelty and emotion may give rise to psychotic phenomenon. It has to be kept in mind that delusions and hallucinations are consciously accessible subjective phenomenon. Patients may not have insight into their illness or its consequences but they are consciously aware of their thoughts and experiences. From that point of view while alterations via subconscious priming may initiate the process of making some stimuli more salient than others – it would become a clinical psychotic experience only in the context of a consciously owned experience.

Thus for the current experiments we considered that salient stimuli are those that pull cognition – particularly including attention, but also orientation, sensory processing and higher processing – and push behaviour – response selection, motor planning monitoring and execution. It was notable that in none of our findings was there a single common brain region or behavioural feature common to all 'salience'. To expect that it would be so is perhaps naïve given the complexity of interacting cognitive processes and brain regions involved.

A neurocognitive system for facilitating the selection of which stimuli to notice and to respond to would be expected to involve all these elements and be able to compare different types of stimuli inputs to coordinate central output processes from attention through to action. Redgrave and colleagues call this a 'Selection Problem' (Prescott, Montes González, Gurney, Humphries, & Redgrave, 2006). Such a problem is likely to be solved by a system that is phylogenetically old, widely connected, and modulated by signals relevant to learning and context. They locate this system the basal ganglia, in functionally segregated, parallel, re-entrant cortico-striato-nigro-thalamo-cortical loops (described in chapter 1(Redgrave, Prescott, & Gurney, 1999). According to their model, competition occurs between stimuli represented through such loops to facilitate allocation of cognitive and behavioural resources, in a 'winner takes all' computation. Competition is on the basis of their relative saliency to

the organism in the current context; salience is therefore the common currency used in this competition, the selection criteria for determining which stimuli 'win' (Redgrave et al., 1999). This process may also therefore best fit with what is termed broadly thought as 'salience processing'.

In the SIT I attempted to weigh the relative saliencies of different stimuli with fMRI in brain regions thought to be critical to psychosis (Lisman & Grace, 2005), and by measuring 2 simple behavioural outputs – reaction time and recognition memory. Both are compound measures of multiple processes, and interpretation in terms of relative stimulus saliencies is not simple. Similarly BOLD related fMRI activation is a surrogate measure of neural activity that may better represent inputs to a region than its spiking output (Logothetis & Wandell, 2004).

The first prediction was that each of the features tested, Reward Novelty and Emotion would elicit behavioural cognitive and neural reactions consistent with salience as conceived of above. A lack of such reactions would weaken support for that feature being salient for the subject being tested. The second prediction was that there would be evidence of interaction between these features – and similarly a lack of interactions would weaken support for salience being multidimensional. The experiment in normal controls was designed to identify the nature and magnitude of these interactions. Finally, the ARMS sample was included to explore whether there was a correlation between these neural changes and clinically expressed symptoms. If no group difference was found then support for the aberrant salience hypothesis, where salience consisted of the features tested, would be weakened for the subjects tested, those at high clinical risk for psychosis.

In fact I found behavioural and neural evidence that each of three aspects of salience –reward, novelty and emotion - modified behaviour and led to significant BOLD related fMRI activation in regions that may in part subserve salience related computations. There were also

a number of significant interactions between these aspects at behavioural and neural levels, suggestive of crosstalk and of integration of these aspects of stimuli, as a unified calculation of relative saliencies would require. Thus salience is not limited to any one element: most salient stimuli are multifaceted, and depend on motivational, affective and novelty context.

More specifically, I found that in healthy participants, emotion slowed reaction times to reward predicting stimuli that would otherwise have elicited a rapid response, and that emotion also reduced subsequent recognition memory for reward-predicting cues. Such interactions may reflect the opposed motivational valence of these cues: reward predicting stimuli have appetitive motivational value, while negative emotional stimuli have aversive motivational value. However, they may also reflect the integration of distinct signals for emotion and reward, coded in separate regions. The fMRI data revealed that there were differences in the nature of reward x emotion interactions in the amygdala and in the posterior hippocampus. In the amygdala, emotion elicited activation to reward-predicting cues but not non-reward cues, whereas in the posterior hippocampus reward related activation was evident for neutral, but not emotional cues.

Interactions between reward and novelty in healthy participants were evident at the neural but not the behavioural level. Reward related activation was greater for novel than for familiar cues in the hippocampus- amygdala, medial and lateral OFC, and midbrain suggesting that these regions may code a 'novelty bonus' for novelty exploration (Kakade & Dayan, 2002). This over-valuing of novel rewards found through exploration of new environments - is well characterised and is thought evolutionally to incentivise the search for new sources of food or mates (Dayan, 1996). A similar interaction has previously been demonstrated in mesolimbic regions, where it also enhanced memory, but only when the reward related dimension was attended (Bunzeck, Doeller, Dolan, & Duzel, 2012; Krebs, Schott, Schutze, & Duzel, 2009b).

There were also behavioural and neural interactions between emotion and novelty. Healthy subjects responded faster to familiar than to novel scenes, but not when they were also emotional. Emotion also boosted the recognition memory effects of familiarisation. At the neural level, interactions were evident both in the ventral striatum, where deactivations to novel (aversive) emotional stimuli resolved with familiarity. Similar effects on deactivation were evident in the dorsolateral prefrontal and frontopolar cortex. The prefrontal cortex has an important role in the moderation of subcortical emotional responses, which may be through reducing amygdala responsivity (Diekhof, Geier, Falkai, & Gruber, 2011), fronto-amygdalar connectivity (Banks, Eddy, Angstadt, Nathan, & Phan, 2007), or via dopaminergic neuromodulation (Kienast et al., 2008). Perhaps here we are seeing this moderation occurring over repeated emotional stimulus presentation, as occurs in fear extinction and with cognitive reappraisal (Smits, Julian, Rosenfield, & Powers, 2012).

Thus in addressing the first question of the study – essentially, what is salience? - I examined responses to three key aspects, and demonstrated that each of these, reward novelty and emotion, altered behaviour and brain activation in a manner that may in part reflect salience processing, and interacted with one another in doing so. However as outlined above, and as will remain until the neurocognition and neuroanatomy of salience processing is resolved, these measures are indirect and serve as approximations for conceptual purposes. Nevertheless I argue that they are approximations that are useful and relevant for systematic testing of aberrant salience hypothesis of psychosis.

5.2 Alterations in salience processing in people at high risk of psychosis

The second phase of this thesis involved the application of this salience framework to people who were experiencing attenuated psychotic symptoms. These symptoms are thought be

related to dopamine driven variations in a salience processing mechanism (Kapur, 2003). This is the first time to my knowledge that different aspects of salience have been systematically studied in an ARMS population, or indeed any group with psychotic symptoms. At present, the published literature is mainly limited to studies of reward salience (alone) in patients with an established psychotic disorder.

In contrast to previous findings in patients with psychosis, which have usually reported reductions in activation during reward paradigms (table 1.1, chapter 1), there was evidence of greater activation during salience processing in subjects with an ARMS than in controls. These hyperactivations were specific to reward anticipation and to the interaction between reward and emotion; there were no clear group differences related to novelty. As reward anticipation activates dopamine neurons (Schultz, 1997) and psychosis is linked to dopamine dysfunction, differences between groups in relation to reward may therefore be unsurprising. Moreover, although the direction of the difference may be different, a differential response in relation to reward is consistent with the findings in patients with psychosis (see chapter 1 table 1.1).

This may reflect a state of 'hyper'-salience during the ARMS, accompanied by moderately elevated striatal dopamine tone (Howes et al., 2009). This may be analogous to an 'activating context' in health, such as when searching for food, or in dangerous situations, where even small stimuli are likely to be important to survival, and have large behavioural contingencies (Grace, 2010). In this situation contextual information is provided by the hippocampus, itself receiving inputs relating to spatial location, novelty, stress and goal relevance. Ventral hippocampal outputs signalling this context release dopamine neurons in the SN/VTA from tonic inhibition by the ventral pallidum, such that salient stimuli can engage larger numbers of neurons in burst firing, producing an increased amplitude of dopamine release (Grace, 2010).

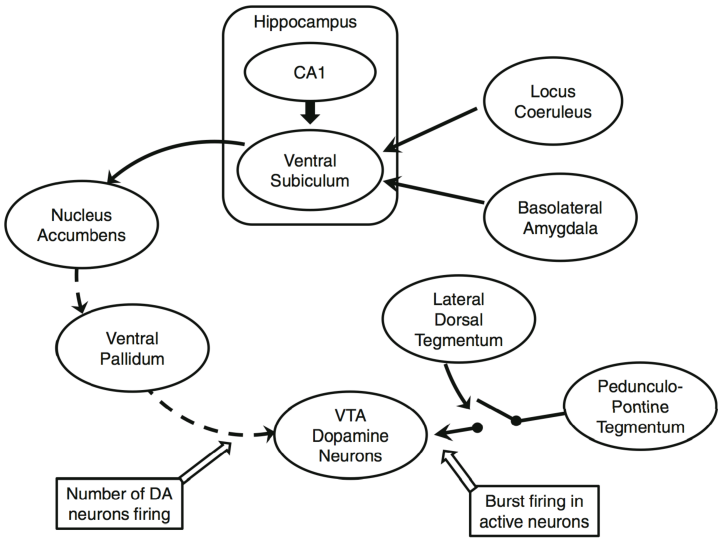

Figure 5.5 Contextual information from the hippocampus incorporate multiple inputs and regulates dopamine tone to alter the overall burst firing output to salient stimuli (from Grace, 2010)

In the ARMS it may be that hippocampal drive to the SN/VTA is similarly altered, so salient stimuli such as visual cues predicting monetary reward lead to greater brain activations. If this process were to progress, the output from the hippocampus may become maximal, to the extent that all of the SN/VTA neurons are active. Under these conditions, even minimally or non-salient stimuli will lead to maximal dopamine burst firing. At this point contrasts measured in behavioural or brain activation terms between salient and non-salient stimuli would be reduced. This would then be equivalent to aberrant salience, as putatively occurs in full-blown psychosis. One could speculate that the transition from the ARMS to frank psychosis might involve a progression as described above, with a change from hyperactivation to salient stimuli, to a reduced response, as described in previous neuroimaging studies. This possibility could be tested by a longitudinal extension of the present study, with the re-scanning of subjects who subsequently develop psychosis.

An important aspect of context is that of aversive emotion or threat, signalled by inputs from structures such as the amgydala and the locus coeruleus (figure 5.5). I found strong activations in both these regions to negative emotional stimuli in both groups. There were also interactions between emotion and reward in the hippocampus and amygdala in both groups,

suggesting that these structures may contribute distinct signals for integration of this contextual information. Such integration would be important in salience calculations to stimuli in different contexts.

Interestingly there was a group difference in this interaction in the ventral striatum, albeit at uncorrected statistical significance. In the ARMS group aversive emotion greatly augmented reward-related activation in the nucleus accumbens. This may reflect a wide range of possible influences on input, including GABAergic projections from the hippocampus, dopaminergic projections from the SN/VTA and output, largely from glutamatergic medium spiny neurons. In controls the augmentation was incremental. This pattern was also seen in the ACC and bilateral insulae, areas that have also been implicated in salience processing (Seeley et al., 2007). That ARMS participants show particular sensitivity to aversive emotion is itself not surprising: emotional disturbances, anxiety and affective disorders are common in the psychosis prodrome (Yung & McGorry, 1996). What is interesting is that such sensitivity was uncovered in aversive emotion augmenting reward related responses; for neutral cues the increased activation to reward cues was incremental, and similar to controls (figure 3.13, 3.14).

This may relate to a connection in people with an ARMS between neurotic symptoms and psychotic symptoms. It also resonates with recent cognitive models of psychosis which have questioned the historical divide between neurotic and psychotic disorders, pointing out that emotional disorders usually precede, and often accompany psychotic symptoms (see Freeman & Garety, 2003). Emotional sensitivity is the hallmark of neurosis; in our sample ARMS participants, who had elevated scores on anxiety and depression scales, but who also were experiencing attenuated psychotic symptoms, did show sensitivity to emotional scenes that in our task had motivational relevance (ie were reward predicting), but not those that did not. A distinction these models do make is that psychotic symptoms unaccompanied by emotional

disturbance may be less functionally disturbing, and less often to clinical 'caseness' or need for care (Krabbendam & Os, 2005). Testing such a sample of those experiencing non-clinical psychotic symptoms would be an interesting extension of the current study. Conversely those with emotional disorders without psychotic symptoms also show sensitivity to emotional cues, but the current results might suggest, not in interactions with reward in the ventral striatum.

5.3 Hippocampal regulation of striatal dopamine and the risk of psychosis

Having attempted to address the first questions- what is salience, how is it processed in the healthy brain and how is this altered in at risk states for psychosis- we come to a final question. What is the role of dopamine in all this? Dopamine is clearly important in motivational and reward-related processes (Berridge & Robinson, 1998; Schultz, 1997), and also in psychosis (Howes & Kapur, 2009), and yet the total role of dopamine modulation even in the healthy brain is far from clear, and complicated by comparisons between measurements of varying temporal and spatial precision of midbrain dopamine neuron firing versus dopamine release in different target regions, in rodents, primates and, using less direct measures, in humans (Heinz, Grace, & Beck, 2009; eg Redgrave, Gurney, & Reynolds, 2008; Ungless, 2004) .

The final part of the thesis examined the relationship of dopamine neurotransmission to normal and abnormal salience processing, by combining PET and fMRI, and informed by the predictions of the Grace lab model of recurrent hippocampal-VTA signalling (Lisman & Grace, 2005) and its alteration as seen in the MAM rodent model of schizophrenia (Lodge & Grace, 2009).

In controls, in the subiculum of the left anterior hippocampus, human analogue of the rodent ventral subiculum, novelty related activation was positively correlated with striatal ^{18}F-DOPA Ki, albeit at trend level, but as would be predicted by the animal model. According to the MAM model, contextual novelty signals generated in the hippocampus increase the proportion of dopaminergic SN/VTA neurons that are in a tonically active state, which increases the 'gain' of dopamine burst firing (Lisman & Grace, 2005). The present data indicated that in humans in vivo, novel cues elicited strong hippocampal activation in both groups, but that there were differences in the relationship between this activation and the level of striatal presynaptic dopamine synthesis capacity, which is most likely a surrogate of dopamine tone. In the ARMS group this was most evident in the associative striatum, in controls the limbic striatum, but this subregion difference did not reach corrected significance. Also correlation is not causation; in rodents the directionality of the Hippocampal-VTA relationship was established through a series of stimulation, blockade and lesion experiments not possible in humans in vivo. It may be for example that levels of dopamine tone in the striatum also reflect dopamine tone in the hippocampus, and boost phasic novelty signals.

Previous studies have shown relationships between questionnaire derived sensation seeking scores and D2/3 receptor density and availability in the midbrain (Zald et al., 2008) and striatum (Gjedde, Kumakura, Cumming, Linnet, & Møller, 2010), and with fMRI novelty-reward interactions in the midbrain and striatum (Guitart-Masip, Bunzeck, Stephan, Dolan, & Düzel, 2010; Krebs, Heipertz, Schuetze, & Duzel, 2011; Krebs, Schott, & Duzel, 2009a). The present data provide the first direct evidence from humans that novelty signalling in the hippocampus is linked to dopamine function in the striatum. Further work will explore this relationship with regard to variation in novelty seeking and sensation seeking personality traits.

Secondly, in controls, in the same subregion of the left anterior hippocampus, activation to negatively valenced emotional cues was negatively correlated with striatal ^{18}F-DOPA Ki. This reflects other findings suggestive of the wider role of dopamine in emotional processing: activations to emotional stimuli correlate with ^{18}F-DOPA measured in the midbrain (Jabbi et al., 2012), ventral striatum (Siessmeier et al., 2006) and the amygdala itself (Kienast et al., 2008). In the hippocampal ROI used in this thesis, and also in the SN/VTA ROI, higher striatal dopamine tone was related to lower activation to aversive emotional stimuli. In these regions dopamine modulation may have an important role in moderating responsiveness to negative emotional cues. In contrast, in the right DLPFC, there were positive correlations between emotion elicited activation and striatal ^{8}F-DOPA Ki. Variation in this dopamine mediated meso-cortico-striatal signalling may help explain inter-individual variation in emotional sensitivity; variations in anxiety and neuroticism scores will be related to fMRI-PET measures in future work.

In ARMS participants however there was no relationship between hippocampal or midbrain activation to emotion and striatal ^{8}F-DOPA Ki, suggesting that the normal coupling between these regions was lost. On the other hand, emotion related activation in the ACC and insulae correlated positively with striatal ^{8}F-DOPA Ki. In these regions, emotion also greatly augmented activation in response to reward in the ARMS group. The ACC and insula are normally involved in the emotional regulation of limbic responses (Etkin, Egner, & Kalisch, 2011) such as during reappraisal (Banks et al., 2007), and also are though to act together as part of a 'salience network' that facilitates switching between default mode and central executive networks (Seeley et al., 2007; Sridharan, Levitin, & Menon, 2008). Understanding the influence of dopamine in these networked operations and their alteration in greater detail requires connectivity analyses; Kienast et al for example found that dopamine function in the amygdala modulated ACC-Amygdalar coupling during negative emotional processing (Kienast et al., 2008). I plan to assess the influence of dopamine on connectivity in the present

data as part of future work. However the current results suggest that ARMS subjects, who have high levels of emotional disorders alongside attenuated psychotic symptoms, and altered interactions between reward and emotional processing, also show alterations in the normal dopamine dependent mechanisms of emotional processing in cortical and limbic regions.

Interestingly there was no relationship in control participants between activation to reward predicting cues in either the hippocampus or the midbrain and striatal ^{18}F-DOPA Ki values. This is in contrast to a wide literature previously discussed relating reward related phenomena to dopamine neuron activity and striatal dopamine release (recently reviewed in Egerton et al., 2011). Similarly there was no evidence of strong ventral striatal activation in controls to reward predicting cues. This may relate to susceptibility artifact in this region, or reduced ratio of signal to noise, but it could also reflect that the reward probe in the SIT is relatively weak – it is a passive reward task, in which outcomes are not dependent on correct choices or timing. This is likely to have a major effect on the strength of reward related mesolimbic fMRI responses (Zink, Pagnoni, Martin-Skurski, Chappelow, & Berns, 2004), and so active timed reward relevant responses are usually a part of reward-only tasks such as the Monetary Incentive Delay Task (Knutson, Adams, Fong, & Hommer, 2001). In the SIT, in which I attempted to compare responses to emotional, reward and novelty aspects of salience, I deliberately made the required response unrelated to any of these 3 aspects. The only task participants faced on each trial was a simple Go-NoGo choice that required detecting whether each scene matched a prior exposed NoGo scene – this ensured attendance to the visual content of each cue. Differential brain and behavioural responses as seen were in this sense passive, and although I attempted to provide 'salience-matched' levels of each aspect, this proved difficult (discussed further below). Nevertheless reward-predicting cues did activate midbrain structures, speed reaction times and improve recognition rates. If a stronger probe of reward had been used a relationship between reward related hippocampal and / or midbrain activation with striatal dopamine measures in controls may have been more evident.

However, these reward-predicting cues, which were presented identically in both groups, led to greater activation in ARMS subjects than in controls. Furthermore, in ARMS participants left anterior hippocampus activation to reward-predicting cues correlated positively with striatal 18-FDOPA Ki values, particularly from the limbic subdivision, a relationship that was not seen in controls. This may relate both to the overactivation seen to reward in ARMS subjects, and the elevated striatal dopamine levels that have been evident in larger ARMS samples studied with F-Dopa PET (Howes et al., 2009).

Again neither the causal direction of this relationship nor the path of influence can be determined from the current analysis. Hippocampal inputs to the striatum may affect striatal presynaptic dopamine synthesis via the multi synaptic pathway onto SN/VTA dopamine neurons, as suggested by Grace and colleagues (Lisman & Grace, 2005), or via a number of alternative routes. Other animal models (e.g. Kellendonk et al., 2006) propose that striatal dopamine dysfunction is primary, and drive positive symptoms of psychosis, and frontocortical dysfunction. The Grace model applied in their MAM treated rodents (Lodge & Grace, 2009) suggests that hippocampal overdrive through this pathway is what drives increased dopamine tone leading to the symptoms of psychosis. The present findings relate hippocampal activation to reward-predicting stimuli with an in vivo measure of dopamine synthesis availability, and in so doing provide limited support for extension of this model to psychotic illness in humans.

Some caveats apply: there were no differences in reward activation in the hippocampus between groups; it is not 'overdrive' in this sense. Similarly dopamine levels were not 'overdriven' - in the subsample that underwent both PET and fMRI scanning there was no group difference in striatal dopamine levels. However, this may have been due to limited statistical power: the samples were not large, and the reward probe used in the SIT was relatively weak. Nevertheless, differences in the relationship of dopamine tone with

hippocampal activation to salient probes may reflect disease mechanisms and herald later changes; in the instance of emotion, the loss of a possibly moderating influence, in the instance of reward the gain of a possibly pathological one.

5.4 Limitations

5.4.1 The nature of the concept of 'Salience'

As discussed above, the concept of salience is widely applied across different fields and is often used as an umbrella term referring to the subjective importance, or prominence of a stimulus relative to the context in which it is embedded. Outside vision research, where summing the physically salient characteristics leads to a definable concept of a "salience map", the concept is widely and variably used. Similarly there is no neural system established for normal salience processing, although the concepts of Redgrave and Grace referenced above may provide a useful neural heuristic framework. The SIT, in constructing a simple behavioural and neural set measure of salience, ie altered reaction, recognition memory and neural activation, is an attempt to advance this position, but has limitations as I readily acknowledge. The design did enable a systematic comparison of 3 key aspects of visual stimuli that have been previously described as salient, and which on testing met the operationalized salience criteria. I was then able to compare healthy reactions to these aspects with a group of subjects experiencing psychotic symptoms, and link these to dopamine function. In doing so I was able to test both of the key steps proposed by the aberrant salience hypothesis (figure 5.1). To my knowledge this is the first time such a multidimensional and systematic examination of the features of normal salience has been attempted to guide testing of the aberrant salience hypothesis in psychosis. It is also the first time such testing has incorporated direct neurochemical measurements of dopamine function.

5.4.2 The utility of the concept of 'Aberrant Salience' for psychosis

A relevant question that arises is to what extent the construct of salience adds to our understanding of the link between dopamine and psychosis. Might it not be more precise for example to simply say that altered dopamine alters reward processing, emotion processing or novelty processing (individually or through several interactions) and this leads to psychosis? What does 'salience' add? Compare figure 5.6 below to figure 5.2 above:

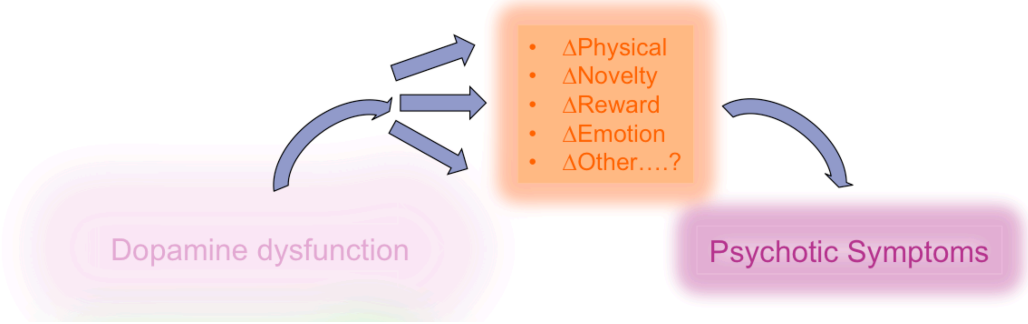

Figure 5.6 – what does 'salience' add?

Indeed there are many studies that demonstrate single dimension abnormalities in all of these elements, and more (see for example table 1.1). The difficulty comes in trying to reconcile these findings with one another, and to find a plausible model that integrates and links these to the formation of psychotic symptoms. Moreover the evidence preceding the current experiment, testing each element in isolation does not permit comparison of the different elements, or the testing of interactions between them.

We could have found some common brain regions across the reward, novelty and emotional paradigms – thereby providing some neurobiological grounding for a common salience network. While these experiments were not designed specifically to address this question – they did have the possibility of identifying such regions. We did not find such a network. This diminishes the appeal of the concept of salience as a unifying concept, because in the absence

of such a common network it becomes an umbrella term which encompasses several processes which share some behavioural features (e.g. enhanced attention, reaction time etc.) and that are mediated/moderated by dopamine.

That being the case, the experiments herein move our understanding forward by providing a simultaneous comparison of these difference aspects, and their interactions. We found that for those at risk of psychosis, the interactions are important, particularly for reward and emotion. This resonates with cognitive models and evidence regarding emotion and emotional distress of aberrant phenomena as critical in driving psychosis (Freeman & Garety, 2003).

5.4.3 Nature of the Salience Integration Task

One limitation of the factorial event related design of the SIT was an apparent loss of power, relative to simpler designs. While facilitating a robust examination of main effects and interactional analyses that were central to my hypotheses, this meant that some of the findings, such as those relating to group differences in novelty and PET, were not optimally corrected for multiple comparisons. Set against this was the focussed anatomical location of the hypotheses, which were informed by the circuits prescribed by the MAM model and the 'salience network', considerably reducing the chances of alpha error. Despite the low to moderate power of some of the analyses, the findings were largely within the expected regions of interest, the hippocampus, amygdala, midbrain and striatum, and in the ACC and insulae. Outside these regions the only other key regions that were sites of activation to both reward and emotion were visual areas, presumably related to the visual nature of the stimuli. This is itself of note, particularly as I was careful to control rigorously for basic visual features of the stimuli such as luminance, colour, movement, contrast, size, and pixel count. This suggests that salient visual stimuli elicit greater occipital activations, particularly in secondary visual areas, supporting findings by Redgrave and colleagues, who point out that dopamine neuron response latencies to such salient stimuli are too fast to code a prediction

error, which would necessarily involve gaze shifting at the very least (Redgrave & Gurney, 2006). Group differences in these areas were not seen however.

A further difficulty with the SIT was the 'titration' of salient-equivalent levels of each aspect studied, as previously discussed. This is necessary in order to reliably compare the behavioural and neural contribution of reward, novelty and emotion to salience processing. However there are no 'chlorpromazine-equivalent' dose conversions for salience. As such the emotional stimuli provided by the IAPS pictures elicited a wider and more powerful range of brain activations that either the reward or novel stimuli. Similarly it was not possible to utilise aspects of reward tasks that ensure more robust responses such as speeded and differential response choices, as this would confound comparisons between reward and other aspects. I could not explicitly model trial by trial expectation or prediction error. However all 3 aspects studied did elicit behavioural and neural differences, and furthermore were the same stimuli for all control and ARMS participants. I was also able to improve the validity of the emotional stimuli by asking each participant to individually rate the emotional arousal caused by each picture, which echoed the ratings of the IAPS reference data.

A final potential criticism of the reward aspect of the SIT could be the absence of ventral striatal activation in controls to the reward predicting cue. This may relate to large signal dropout due to susceptibility artefact in this region, particularly more anteriorly (Vargas, Delavelle, Kohler, Becker, & Lovblad, 2009). It could also reflect an incomplete transfer of reward related activation from the outcome to the cue resulting from the partial reinforcement schedule. The most likely explanation, as discussed above, is the passive nature of the reward aspect of the task, necessary to ensure equivalent attention was given to each of the three aspects of salience studied.

Lastly, the behavioural indices of the SIT whilst simple were compound measures of multiple cognitive processes and did not readily lend themselves to detailed interpretation, particularly

with respect to brain level fMRI and PET findings. Although there were group differences in behaviour, and these were strongest for the reward and emotion aspects studied, the direction of these differences was sometimes opposite to fMRI findings, and I did not directly relate behavioural measure to fMRI or PET.

5.4.4 Ultra High Risk population

One common difficulty with studying mechanisms of the onset of any disease of low incidence is finding enriched samples that yield high transition rates. The clinical ultra high risk for psychosis strategy is one of the most successful strategies for psychosis but still yields a minority of transitions to psychosis over a limited follow-up time period, particularly when patients are being treated to actively prevent such a transition (McGorry et al., 2009; Yung et al., 2007). One criticism of this strategy is therefore that most of the population studied will in fact not go on to develop full psychotic disorder. This has clear implications for power in the study, as the 'disease' group is being effectively diluted by participants who will turn out to be in a sense false positives. Any group related difference between ARMS and control samples is therefore likely to either reflect a large effect in the subgroup who go onto develop psychosis, or be related to factors other than those specifically linked to transition, such as disease susceptibility, or general factors such as functional impairment, distress and so on. Set against this is one key attribute of the *clinical* high risk strategy, which is that patients are mostly recruited on the basis of active attenuated psychotic symptoms of a minimum severity, frequency and duration. These symptoms, though not reaching the level seen in frank psychosis, cause marked distress and lead sufferers to seek clinical help. The mechanisms underlying these symptoms are likely to be similar to those that underlie full-blown psychotic symptoms, as they are pheonomenologically similar, and studying 'attenuated' psychotic symptoms in and of themselves is therefore of great interest (Wood et al., 2004). Following up the ARMS sample to determine their clinical outcomes is of course central to the broader

study and will be a part of ongoing work. Testing the SIT in a further sample of first episode psychosis patients will also help validate the findings.

5.4.5 PET study

Two separate samples have confirmed that ARMS participants show elevations in striatal ^{18}FDOPA Ki that are intermediate between healthy controls and participants with a first episode of psychosis (Egerton et al., 2012; Howes et al., 2009). In the current sample there was not a significant group difference in striatal FDOPA ki. However, this may be due to the relatively small number of subjects who had a PET scan (and a lack of sufficient statistical power). As Ki values in ARMS subjects who later develop psychosis are higher than in those who do not (Howes et al, 2011), another possibility is that the proportion of the present sample that is destined to become psychotic is relatively small. This issue will be addressed through clinical follow-up.

5.5 Possible Mechanisms

An important finding of this thesis is the confirmation in the healthy controls of a relationship between anterior hippocampal activations to novelty and emotion and striatal dopamine levels. This is largely as predicted by the Grace model (Howes et al., 2012; Lisman & Grace, 2005). Similarly I found significant departures from these relationships in participants at high clinical risk for psychosis, experiencing attenuated psychotic symptoms. There was both overactivation to reward in the striatum, and a positive relationship between hippocampal signalling to reward and striatal presynaptic dopamine levels, that was not present in controls. This is some of the first evidence from humans that abnormal hippocampal drive of midbrain dopamine output may underlie the striatal hyperdopamergia thought to lead to positive psychotic symptoms, that was proposed on the basis of animal models (Grace, 2011). The

findings also suggest that this abnormal hippocampal drive may be associated with altered reward salience processing.

What could be the neurochemical mechanism underlying hippocampal overdrive? Interneuron dysfunction has been proposed as one such mechanism, leading to a loss of tonic inhibition of glutamatergic projections from the hippocampus through the striatum and on to the midbrain. This could result from hypofunctional NMDA receptors located on inhibitory GABAergic interneurons, as proposed by Olner and Faber (1999; Stone, Morrison, & Pilowsky, 2007). This was originally thought to involve glutamatergic projections from the prefrontal cortex and thalamus, but the present data implicate projections from within the hippocampus, as proposed more recently by Grace and colleagues (2011).

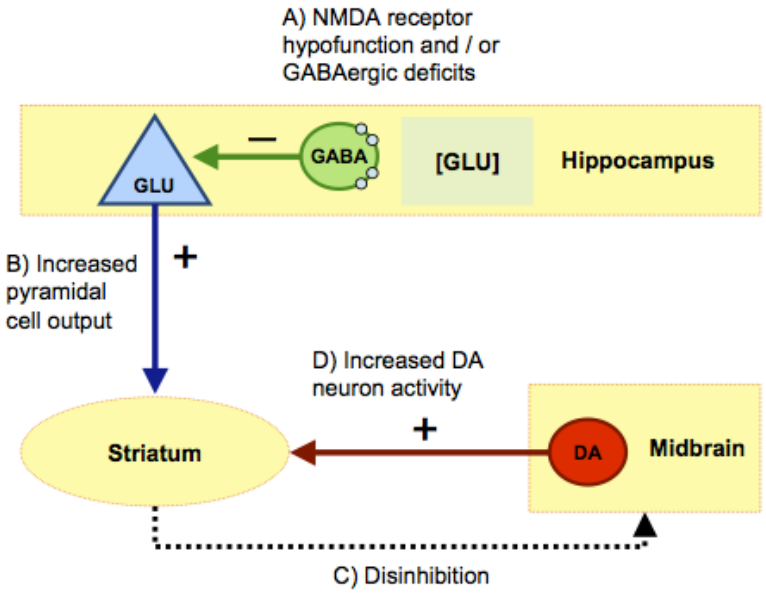

Figure 5.4 - Relationship of hippocampal interneuron dysfunction to increased striatal dopamine activity

An alternative mechanism involves GABA receptors in the hippocampus. GABA receptors are of several subtypes, distributed widely throughout the brain. The alpha 5 subtype is mainly located within the hippocampus and connected limbic cortex. Grace et al suggest that

this particular receptor may be the site of the hippocampal abnormality, based on a series of stimulation and blockade experiments showing that hippocampal outputs drive midbrain dopamine neurons, and evidence that there are reductions in hippocampal parvalbumin containing GABA interneurons in schizophrenia (G. P. Reynolds, Abdul-Monim, Neill, & Zhang, 2004).

The role of GABA in this model could be assessed directly by measuring hippocampal GABA levels in vivo using neuroimaging. However, there are technical challenges involved in this work - MRS signalling in the medial temporal cortex is noisy due to high susceptibility artefact and PET GABA ligands are non receptor subtype specific. One study using a relatively GABA-Alpha5 selective ligand, ^{11}C-Ro-15 4513 found no difference in hippocampal GABA levels between participants with schizophrenia and controls (Asai et al., 2008), but did identify a relationship between symptoms and GABA levels in the prefrontal cortex. More recent developments in analysis of pharmacokinetic profiling may facilitate extraction of the alpha 5 subtype located within the limbic cortex with greater specificity (Lingford-Hughes et al., 2002).

Consideration of brainwide abnormalities has been largely outside the scope of this thesis. However the finding of reward-emotion interaction group differences in the regions corresponding to the Salience network (ACC and bilateral insulae) prompts some interesting speculation and further questions. White et al examined functional network connectivity between the salience network and other networks identified during a somatosensory task, and found reduced connectivity between the ACC and insula, and between this network and the default mode network (White 2010). The present findings link to these in locating different reward-emotion interactions in those at risk of psychosis in this network, with altered relationships with striatal dopamine levels. Further work will elucidate the relationship of this network dysfunction to the wider brain network.

5.6 Implications and Future Work

There are a number of important extensions of this work that will further validate and extend the main findings leading to possible translational benefit.

5.6.1 Follow-up of UHR subjects

All ARMS participants will be followed up clinically for a minimum of 3 years. This period is the most timeframe for transition to psychosis following the detection of an ARMS , in previous larger samples with long-term follow-up 20-40% of subjects had transitioned within this period (figure 5.5 Fusar-poli et al., 2012). Baseline comparisons of those who later transitioned will be made on behavioural, fMRI and PET measures, particularly with regard to hippocampal -dopamine relationships.

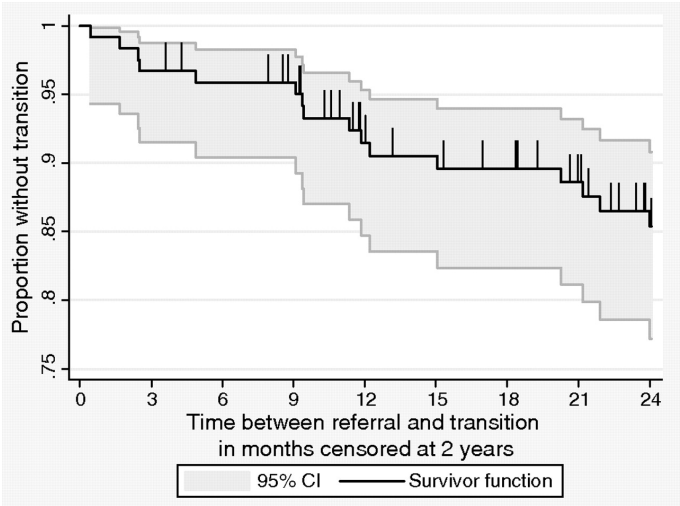

Figure 5.5 Survival curve for transition to psychosis from a recent OASIS cohort. Figure adapted from (Demjaha, Valmaggia, Stahl, Byrne, & McGuire, 2012).

5.6.2 Connectivity analysis of Salience Network

Prompted by the finding of differences during the interaction of reward an emotional processing in the ARMS, I plan to extend the analysis of whole brain network connectivity. Resting state scans in all participants will be used to identify key brain networks, and examine the relationship of these networks to the salience network during rest and during the SIT task. I also plan seed based connectivity analyses of components of salience processing identified during our task.

5.6.3 Testing of SIT in First Episode Psychosis subjects

Similarly, a 3rd experimental group with a First Episode for Psychosis will be recruited and tested with the SIT. This will provide an important cross sectional comparison group for the findings between ARMS and control participants. In particular I will be interested in testing whether first episode patients display aberrant salience, as opposed to the hypersalience that was evident in the ARMS sample.

5.6.4 Glutamate MRS

Also of value would be the collection MRS data in all of the participants in this thesis from several areas of interest, the ACC, DLPFC, Hippocampus and Thalamus. These will be analysed in relation to Salience order to further elucidate the underlying mechanisms and help determine whether GABA or NMDA Glutamate receptor dysfunction drives the abnormalities in ARMS participants.

5.6.5 Alpha-5 GABA imaging using MRS and PET

Although quantifying GABA levels has proved difficult using MRS (Edden & Barker 2007) I plan to test GABA function in the hippocampus using two methods. First is the recently

developed MEGAPRESS sequence that has been validated in healthy controls (Edden & Barker 2007). This has the disadvantage of being non receptor selective. Therefore I will also use the ^{11}C Ro-15 GABA PET ligand which is relatively selectively for the Alpha5 subunit, located primarily in the hippocampus (Momosaki, Hosoi, Abe, & Inoue, 2010; Myers et al., 2012). Although one study has shown a lack of difference between participants with schizophrenia and controls (Asai et al, 2008), novel pharmacokinetic modelling techniques that allow more reliable separation of alpha 5 and alpha 1 signals will be employed.

5.6.6 Towards novel treatment targets for schizophrenia

The rationale for work understanding disease mechanism, both from a cognitive and a neuropathophysiological point of view is to improve treatments and outcomes for those with psychosis, which remain poor (van Os & Kapur, 2009). Evidence of the staged development of alterations in salience processing particularly in motivational and emotional systems may help further inform cognitive therapeutic approaches to psychosis treatment and prevention, that are stage specific (McGorry et al., 2009). They may similarly aid understanding of the origin and development of psychotic symptoms for carers of those suffering from psychosis, and for the wider public (van Os, 2009).

Specific work relating to the neurofunctional and neurochemical bases of altered salience processing and psychosis may help provide new pharmacological treatment targets. The current study provides support for the predictions of a recent influential rodent model of psychosis highlighting the relationship of disordered hippocampal signalling relating to altered striatal dopamine. Specifically these data supports the idea that dopamine dysfunction is secondary to a primary problem 'upstream' in the hippocampus. This may explain why dopamine blockade is only partially effective. It may be beneficial to develop drugs that target the hippocampal dysfunction, and these may be GABA or Glutamatergic. Most current drug development is on such non-dopaminergic drugs.

5.7 Final Conclusions

Selecting which stimuli to attend and respond to requires a 'common currency': salience. Salient stimuli pull cognition and push behaviour, are multifaceted, motivationally and affectively valenced. During the development of psychotic symptoms, a period of 'hyper'salience may precede later aberrant salience and full blown psychosis, particularly through an increased sensitivity to reward and aversive emotion. Salience processing occurs in a subcortical network involving the medial temporal lobe, midbrain and basal ganglia. Hippocampal signals of salient emotional and novel stimuli relate to striatal dopamine signalling in health, which become dysregulated and driven by reward during the development of psychotic symptoms. These data support the predictions of both the aberrant salience model of psychosis and also the MAM model, that dopamine dysfunction relates to abnormalities upstream in the hippocampus. This has implications for understanding mechanisms of psychotic illness, and for the development of new cognitive and pharmacological treatments.

Supplementary material

HC group only fMRI contrast	Striatum	+/-	k	t	z	p(unc)	p(FWE WB)	x,y,z (mm)	Location
Reward cue	Whole	+/-	NIL						
	Limbic	+/-	NIL						
	Associative	+/-	NIL						
Reward outcome	Whole	+/-	NIL						
	Limbic	+/-	NIL						
	Associative	+/-	NIL						
Novelty	Whole	pos	NIL						
		neg	NIL						
	Limbic	pos	27	5.57	3.84	<0.0001	0.634	42 -40 61	R Parietal
			78	5.12	3.66	<0.0001	0.808	-30 -10 -8	L Ventral Putamen
			27	4.36	3.31	<0.0001	0.979	33 35 43	R DLPFC
			15	4.03	3.14	0.001	0.996	33 26 -20	R IFG
			28	3.89	3.07	0.001	0.998	-12 -67 49	L Precuneus
			9	3.87	3.06	0.001	0.999	42 17 -5	R Insula
		neg	37	4.88	3.55	<0.0001	0.885	-48 -22 22	L Insula
	Associative	pos							
		neg	5	4.07	3.16	0.001	0.995	-54 -22 22	L MTG
			22	3.97	3.11	0.001	0.997	-6 50 22	L MFPC
Emotion	Whole	pos	15	3.77	3	0.001	0.999	42 44 19	R DLPFC
		neg	31	4.8	3.52	<0.0001	0.879	-51 -55 22	LSTG
			4	4.11	3.19	0.001	0.989	-21 -82 -8	
	Limbic	pos	29	5.83	3.94	<0.0001	0.496	36 41 34	R DLPFC
		neg	773	7.16	4.39	<0.0001	0.161	18 -37 -14	Cerebellum
	Associative	pos	7	3.61	2.91	0.002	1	39 44 22	R DLPFC
		neg	68	5.08	3.64	<0.0001	0.775	45 -49 16	ITG
			42	4.55	3.4	<0.0001	0.933	-54 -7 -17	L MTG
			35	5.93	3.98	<0.0001	0.447	51 -4 -17	R MTG
			17	3.51	2.85	0.002	1	-27 -82 -11	L Occipital gyrus

Supplementary table 4.1 Whole brain interactions between fMRI activations to Reward, Novelty and Emotional salience and 18-FDOPA PET Striatal Ki in healthy controls

ARMSvHC Whole Brain Analysis								
fMRI contrast	PET striatal ROI	k	t	z	p(unc)	p(FWE WB)	x,y,z {mm}	Location
Reward	Whole	57	3.93	3.42	<0.001	0.564	42 -1 -35	R temp pole
	Limbic	NIL						
	Associative	32	3.73	3.28	0.001	0.703	33 2 -35	R temp pole
Novelty	Whole	7	3.46	3.09	0.001	0.961	9 -34 -32	low MB
		6	3.18	2.88	0.002	0.994	-6 56 34	DMPFC
		3	3.08	2.8	0.003	0.997	6 53 40	DMPFC
		12	3.54	3.14	0.001	0.942	-60 -43 16	STG
		17	3.2	2.89	0.002	0.993	-24 -10 -2	L Pallidum/Putamen
	Limbic	NIL						
	Associative	6	3.63	3.21	0.001	0.889	9 -34 -32	low midbrain
		10	3.22	2.9	0.002	0.988	-6 56 34	DMPFC
Emotion	Whole	NIL						
	Limbic	357	4.19	3.59	<0.001	0.579	3 -73 40	R Precuneus
			4.17	3.58	<0.001	0.589	-3 -70 28	L Precuneus
		129	3.96	3.44	<0.001	0.73	6 38 7	R ACC
		10	3.76	3.3	<0.001	0.847	33 17 52	R DLPFC
		80	3.69	3.25	0.001	0.882	48 -31 19	Insula/Parietal Operculum
		29	3.48	3.1	0.001	0.954	-24 50 19	L MFG
	Associative	20	3.76	3.3	<0.001	0.852	-3 -34 -11	L Midbrain (PAG)

Supplementary table 4.2 ARMS v HC whole brain interactions between fMRI activations to Reward, Novelty and Emotional salience and 18-FDOPA PET Striatal Ki in healthy controls

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